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THE STORY OF THE DEVELOPMENT OF OUR IDEAS OF CHEMICAL MEDIATION OF NERVE IMPULSES.*

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The story of the growth of our knowledge that nerve impulses affect smooth muscle, cardiac muscle and some digestive glands by setting free a chemical mediator I have chosen for a variety of reasons. First, it is a relatively new story, descriptive of recent advances of knowledge, that promise important fresh insight into still unknown realms of physiology and medicine. Again, it illustrates to an unusually striking degree the ways in which science may progress, with the early bold projection of novel ideas, the hesitant and tentative groping of investigators in unfamiliar territory, the performance and reporting of experiments the full significance of which was not at the time well understood, the occurrence of flashes of perspicacity, the slow accumulation of facts that lead to conviction, the illumination of old, dark mysteries in the light of the new truth, and the forward look toward further exploration in the twilight zone of ignorance that surrounds us. In the brief time available I shall not be able to tell the story in full detail; instead, I shall lay emphasis only on its salient features.

The meaning of chemical mediation of nerve impulses is made clear by reference to the first intimation of its existence. In 1904 T. R. Elliott,[1] then a young student of physiology at Cambridge, England, was struck by the fact that long after sympathetic nerves had been cut and degenerated, the structures previously innervated

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by these nerves (smooth muscle, for example) respond in a characteristic manner to adrenin—contracting in response to this agent where sympathetic impulses formerly caused contraction, and relaxing where they formerly caused relaxation. Obviously the adrenin did not affect any structure dependent on the peripheral nerves, for they had degenerated. Elliott thereupon offered the highly important suggestion that whenever a sympathetic nerve impulse arrives at a smooth-muscle cell, it may liberate adrenin locally in the cell, and that this adrenin acts as a chemical step in the process of stimulation. In Elliott's own words, adrenin "might then be the chemical stimulant liberated on each occasion when the impulse arrives at the periphery." The fact that adrenin from the adrenal glands mimics the action of sympathetic impulses would thus be explained; it is the same substance as that which, in Elliott's idea, serves locally as an intermediary between the impulses and the special reacting mechanism in the cell.

As already noted, in some smooth-muscle cells sympathetic impulses, and also injections of adrenin, cause contraction and in others relaxation. The impulses can be artificially produced by electric shocks, and thus they can be made the same in duration and frequency for the two opposite effects; and the adrenin likewise is the same for both. How, then, may these quite contrary effects of the same agents be explained? In 1905 Langley,[2] the Cambridge physiologist, puzzled by the facts, published the hypothesis that in reacting cells two sorts of "receptive substances" exist, excitatory and inhibitory. When adrenin reaches a cell, he surmised, its action is determined by the kind of receptive substance there present; if it unites with the excitatory substance contraction results, and if with the inhibitory, relaxation. As we shall see, many years later Langley's idea received experimental support.

Another step in the development of the concept of chemical mediation of nerve impulses was taken in a research published in 1906 by Howell[3] of Baltimore. The resemblance between the inhibition of the heart induced by potassium salts and that induced by vagal stimulation had led Bottazzi,[4] in 1896, to suggest that the two are identical in character. Martin[5] had brought forward further evidence for that conclusion in 1904. Working on the idea that the vagus might exert its inhibitory influence through the agency of potassium compounds, Howell found that the efficacy of vagal impulses varied with the amount of potassium salt in the perfusing fluid, and he drew the inference that the impulses act indirectly by increasing the amount of diffusible potassium compounds in the heart tissue. That was in 1906. Two years later Howell and Duke[6] reported that vagal stimulation causes an increase of the potassium content of Locke's solution perfused through an isolated mammalian heart, and they regarded the results as favoring the view that vagus nerves exercise their cardio-inhibitory

influence through the direct action of diffusible potassium compounds which vagal impulses set free. Although the concept of chemical mediation is here clearly expressed, and experiments justifying that concept are reported, neither the theory of potassium inhibition nor the data in support of it have fitted into the progressive developments which have led to our present understanding. We now know that an inhibitory chemical substance is, indeed, readily liberated in cardiac tissue by vagal impulses, and that like those impulses, but unlike potassium salts, it is blocked by atropin. I must not, however, anticipate events!

The next suggestion which finds its place in this historical sequence was published by Dixon and Hamill,[7] in 1909. They drew attention to the resemblance between the effects of nerve stimulation and the effects of certain drugs. "There is no inherent difference," they wrote, "between the action of muscarine on the heart on the one hand, and electrical excitation of the vagus nerve on the other. So similar are the two effects that it is not unwarrantable, in the absence of any evidence to the contrary, to assume that they are brought about in the same way. If it is permissible to argue from analogy, there is reason in the suggestion that excitation of a nerve induces the local liberation of a hormone which causes specific activity by combination with some constituent of the end organ, muscle or gland." Note that this idea is essentially the same as that expressed earlier by Elliott, the only difference being that muscarin is proposed as the intermediary for vagal impulses, whereas Elliott had suggested adrenin as the chemical agent for sympathetic impulses. These guesses by Dixon were not put forth without efforts to secure an experimental basis for them. It appears that he had killed animals by pithing them, had let them bleed, and then had stimulated the vagus nerves for half an hour. An extract of the heart, made thereafter, "was found to have the power of inhibiting the frog's heart, and like muscarine the effect was completely antagonized by atropine." This highly suggestive observation Dixon[8] published in an obscure journal, *The Medical Magazine*, in 1907. I learned of it by reading the obituary notice of Dixon published by Gunn,[9] in 1932. Gunn testifies that he once asked Dixon why he dropped this research in which he had made such interesting beginnings and received the reply that he was deterred by the universal skepticism with which his views were received!

It is probable that reports by Dale[10] and by Dale and Ewins[11], in 1914, played a rôle in the further development of our knowledge of chemical transmission of nerve impulses. Before their work is detailed, however, mention should be made of a discovery reported about 8 years before by Hunt and Taveau.[12] Noting that in aqueous extracts of the adrenal gland a blood-pressure reducing substance was present which, on chemical treatment, disappeared

as the cholin content increased, Hunt had inferred as early as 1901 that in the extract there might be an esterlike precursor of cholin. With Taveau's coöperation a number of esters were made, among them acetylcholin which proved to be a most remarkable substance, being a hundred thousand times more active than cholin in causing a fall of blood pressure, and a hundred times more active in that effect than is adrenalin in causing a rise. In the reports by Dale in 1914 the fact was brought out that certain ergot extracts produced changes in the body closely resembling those produced by muscarin, and that the agent responsible for them was acetylcholin, *i. e.*, the muscarin action might be due to the presence of a cholin ester in its chemical structure. The effects observed when acetylcholin was injected included, Dale stated, a "pronounced vagus-like inhibition of the heart, and various other effects of stimulating nerves of the cranial and sacral divisions of the autonomic system—secretion of saliva, contraction of the œsophagus, stomach and intestine, and of the urinary bladder." These effects, which were very brief, were abolished by small doses of atropin. Here we have definitely the intimation that acetylcholin mimics the action of parasympathetic nerve impulses, much as adrenin mimics the action of sympathetic impulses. It seems probable that this hint would have been promptly seized and worked upon if the World War had not forced the attention of investigators to more urgent matters.

It is noteworthy that up to this time there was no satisfactory experimental evidence supporting the hypotheses which had been offered. Indeed, 7 years passed before any further progress was made, and then, in 1921, two researches were published, one a contribution the significance of which was not appreciated at the time, and the other a recognized forward move in the developing course of events. The former research was conducted by Uridil and myself; the latter by Otto Loewi, the Austrian pharmacologist.

Uridil and I[13] were concerned primarily with a criticism which had been brought by Stewart and Rogoff[14] against my use of the denervated heart as an indicator of the secretion of adrenin. I[15] had reported that a stimulus applied to the splanchnic nerves caused the denervated heart to beat faster if the adrenal glands were intact, but that after removal of the glands the same stimulus had a minor effect. Stewart and Rogoff, on the other hand, noted that, with the glands removed, direct splanchnic stimulation still caused a considerably faster rate of the denervated heart—a result which, they declared, they were not called upon to explain, but which they attributed chiefly to the attendant rise of arterial pressure. Since it was well known that variations of arterial pressure would not alter the rate of a well-nourished isolated heart, their suggestion was lacking factual support. We were convinced that there was "some other hitherto unknown factor at work

causing the faster rate," and we started out to find it. Our experiments led to evidence that splanchnic stimulation, after the adrenals are extirpated, causes the discharge of a substance from the liver, a substance which, like adrenin, accelerates the heart and raises blood pressure, and that these effects are slight if the animals have been fasting but considerable if they have been digesting meat. Thus was explained the discrepancy between the earlier results which I had obtained—for I had used fasting animals—and the results of Stewart and Rogoff, who had not paid attention to the digestive state. The centering of interest on conditions which affect secretion from the adrenal medulla unfortunately led to a prolonged neglect of our suggestive observations. Not until years later did it become clear that the cardio-accelerator substance from the liver has properties linking it with Elliott's suggestion of an adrenin-like mediator of sympathetic nerve impulses.

In conversation Loewi has given an interesting account of the origin of his experiments. One night, having fallen asleep while reading a light novel, he awoke suddenly and completely, with the idea fully formed that if the vagus nerves inhibit the heart by liberating a muscarin-like substance, the substance might diffuse out into a salt solution left in contact with a heart while it was subjected to vagal inhibition, and that then the presence of this substance might be demonstrated by inhibiting another heart through the influence of the altered solution. He scribbled the plan of the experiment on a scrap of paper and went to sleep again. Next morning, however, he could not decipher what he had written! Yet he felt that it was important. All day he went about in a distracted manner, looking occasionally at the paper, but wholly mystified as to its meaning. That night he again awoke, with vivid revival of the incidents of the previous illumination, and after this experience he remembered in his waking state both occasions. He set up a frog heart filled with Ringer's fluid, and after inhibiting the heart by stimulating the vagus nerve, found that the fluid had acquired a new property—that of being able to induce in another frog heart typical inhibitory vagal effects. Furthermore, he found also that when the sympathetic nerves were stimulated, to make the heart beat more rapidly, the Ringer solution in contact with it became endowed with cardio-accelerator power, *i. e.*, an agent was added to it, which, like adrenin, had sympathomimetic influence.[16] Although, at first, these observations were not confirmed by some investigators, they have been wholly substantiated by others, and at present the support for Loewi's work may be regarded as conclusive.

The nerves supplying the heart are representatives of the widely distributed fibers of the parasympathetic and sympathetic divisions of the autonomic system. The question naturally arises, can the phenomena noted in the heart be repeated elsewhere in the body?

That has been found to be true. Stimulation of smooth muscle and likewise glands causes the appearance of sympathomimetic and parasympathomimetic substances in neighboring fluids. Thus, Engelhart[17] noted that after he had excited electrically the oculomotor nerve and induced contraction of the smooth muscle of the ciliary body and the iris, the aqueous humor of the eye had a new vagus-like action on the tortoise heart. Furthermore, Bain[18] has reported that fluid flowing through the bloodvessels of the tongue of a dog, while the smooth muscle of the vessel walls was being relaxed by exciting the lingual nerve, was endowed with the ability to provoke activity in the smooth muscle of the rabbit intestine. And finally, Gibbs and Szelöczey[19] have demonstrated that the perfusing fluid, which has passed through the vessels of the cat's submaxillary gland during periods of stimulation of the chorda tympani nerve, can cause a fall of blood pressure, excitation of a salivary flow, inhibition of the isolated frog heart and augmented intestinal movements. In all these instances the structures were originally affected by parasympathetic nerves, and the salt solutions in contact with the structures were made capable of producing characteristic parasympathetic effects on other structures. The analogy with Loewi's frog heart experiments is evident.

Similar evidence extended in the sympathetic system Loewi's original evidence of chemical transmission of nerve impulses. Thus Brinkman and Van Dam,[20] Külz,[21] and also Lanz[22] found that the Ringer solution from a heart which has been accelerated by sympathetic stimulation exerts a typical sympathetic inhibitory effect on gastric peristalsis—just the sort of effect that is produced by injection of adrenin. Furthermore, Finkelman[23] showed that if Ringer's solution is allowed to run over a pulsating strip of rabbit intestine still supplied with its mesenteric nerves (piece A), and to drop thence on another strip of pulsating intestine (piece B), the solution has a new property, as piece A is inhibited by nervous stimulation—then piece B on which the solution drops is also inhibited.

In all the experiments hitherto cited, except those of Uridil and myself,[13] the mode of transfer of the chemical agent that mimics the action of sympathetic or parasympathetic nerve impulses is by way of salt solutions. This condition was criticized in 1929 by Demoor,[24] the Belgian physiologist, who pointed out that the irrigations which are part of the methods employed "may create new conditions of existence for the tissues, conditions accompanied by permeabilities which do not exist in physiologic states, and that the escape of vagal and sympathetic substances, though proved experimentally, may not occur normally." This prudent skepticism has been met by evidence that the substance representing parasympathetic impulses can circulate in the blood under nearly normal conditions, and that the substance representing sympathetic impulses can circulate under conditions which are wholly normal.

In order to understand this advance we must consider first the nature of the so-called "vagus substance." Studies by Loewi and others[25] have shown that it is dialyzable, that it is stable in an acid but not in an alkalin medium, that it is rapidly rendered inactive by a blood or tissue esterase, and that, if thus altered, the activity can be restored by acetylation. In all these respects the vagus substance is like acetylcholin—a fact that recalls Dale's observation in 1914, that acetylcholin mimics the functions of parasympathetic impulses. Another feature common to vagus substance and acetylcholin is that each is protected from inactivation by physostigmin. The rapid destruction of the substance in blood can thus be largely avoided. Such was the strategy employed by Babkin, Alley and Stavracky[26]—during each experiment they injected physostigmin repeatedly in doses sufficient to assure success. With that provision they found that when they caused, say, the left submaxillary gland to secrete by stimulating its chorda tympani nerve, they obtained slightly later a secretion from the right submaxillary gland, which had been denervated. The only means of communication from one gland to the other was the circulating blood; and when the vein conveying blood from the stimulated gland was closed, repetition of the stimulus did not produce its regular effect on the other side. Not only secretion, but also dilation of the blood vessels on the denervated side was recorded, and attendant thereon was a fall of blood pressure. All these results are characteristic of both parasympathetic discharge and the action of acetylcholin. They not only support the other evidence that when parasympathetic nerves are excited they produce their effects by liberating a mediating substance, but also they show that this substance, protected by physostigmin, can be carried without destruction in the circulating blood, and can mimic elsewhere in the organism the effects of parasympathetic impulses.

The observations of Babkin and his collaborators were published in 1932. In 1931, Bacq and I[27] reported that a substance mimicking the effects of sympathetic impulses was carried in the blood stream from a stimulated region and could produce typical adrenin-like effects elsewhere. This result solved a mystery which had puzzled workers in our laboratory for some years. In order to make this part of the story clear, I must return again to the controversy with Stewart and Rogoff, previously referred to.

The Cleveland investigators had declared that the secretion of adrenin from the adrenal medulla is steady and unvarying, whereas our group contended that asphyxia, "painful" stimulation and emotional excitement cause a special discharge of adrenin. Each side brought out supporting evidence, but evidence obtained by different experimental procedures. In order to secure more facts bearing on the controversy, Lewis, Britton and I[28] devised a method of separating the heart surgically from the central nervous system while leaving the organism otherwise in a quite normal state. The

heart in these circumstances, though not subject to nervous control, may be strikingly influenced by changes in the circulating blood. For example, it is exquisitely sensitive to an extremely minute increase in the concentration of adrenin. By use of the denervated heart it was possible to prove that asphyxia and "painful" stimuli, and also motion and emotion, induce medulli-adrenal secretion, for the faster heart rate evoked by these states fails to occur after the adrenal glands are rendered inactive. Thus, before adrenal inactivation, emotional excitement with attendant struggle might cause a high rise in the pulse rate—100 beats per minute or more—beginning within a few seconds from the start of the struggle; but after the inactivation, this quick, sharp rise almost wholly disappeared. I shall not detail further the evidence for special secretion of adrenin; it is sufficient to remark that after many years no one has confirmed the results reported by Stewart and Rogoff, and that numerous investigators, using various methods, have found, as we did, that medulli-adrenal secretion is influenced by any situation which calls the sympathetic system into activity.

Now, although the quick, sharp rise in the rate of the denervated heart was absent after the adrenal glands could no longer participate in the response, there was a slow, moderate increase of the rate. Shortly after a brief excited struggle, for example, the rate began to be faster, and at the end of about *3 minutes* it might be elevated by 25 or 30 beats per minute. This strange phenomenon, first noted in 1926, remained for years unexplained. What was the cause of it? In the efforts to find an answer to that question I was ably helped by Newton and Zwemer.[29] We perceived clearly that the phenomenon must have been due to some change in the circulating blood, for that alone connected the heart functionally with the rest of the organism. Previous experiments had proved that it did not result from increased blood pressure, from increased blood temperature, nor from metabolites thrown off by active muscles. It seemed most probably the effect of some internal secretion. Successively we removed not only the adrenal medulla but also accessory chromaffin tissue lying between the kidneys, we ruled out the adrenal cortex, we set aside the liver by severing the hepatic nerves, we excluded a possible rôle of the alimentary canal by extirpating the abdominal sympathetic chains—and still struggle made the heart respond in a more rapid pulse. We removed the pituitary body, we disconnected the thyroids and parathyroids from the spinal cord by taking out the cervical sympathetic strands—and still the mysterious acceleration persisted. Though much puzzled by the situation we treasured the certainty that excitement and struggle cause discharge of sympathetic nerve impulses. At the stage now reached in our efforts to solve the riddle, only short strands of the sympathetic were still present—the remnants in the lower thorax. Might it not be true that impulses discharged ***via***

these few ganglia were somehow causing the heart to beat more rapidly? We removed them—and the strange cardiac acceleration ceased! Vigorous struggle sent the beat up perhaps 4 beats per minute, but not 25 or 30. Observe that we now had a new organism in the history of biology—a higher vertebrate without any sympathetic system. Interest in the altered physiology of such a creature temporarily turned our attention away from the curious, slow cardio-acceleration which we had started to investigate, and not until 1930 was that trail sought again and followed.

That the remnants of the sympathetic ganglia in the lower thorax distribute fibers to the liver or the heart seemed quite improbable. It appeared more likely that when they discharged impulses into the skin region they produced something which entered the circulating blood and affected the heart.

In order to test this idea Bacq and I[27] prepared animals with denervated hearts, and then stimulated the lower abdominal sympathetic chains, isolated from the spinal cord. These chains innervate only smooth muscles—those of the hairs and the blood vessels, especially in the region of the tail. Of course the only functional connection between the denervated tail and the denervated heart was the vascular system. We found that when we stimulated the sympathetic chains and caused erection of the tail hairs, there followed in about 2 minutes a marked elevation of arterial blood pressure and in about 3 minutes an increase of heart rate of 18 beats per minute. When the bloodflow into and out from the tail was blocked the same stimulus had no effect, until the block was removed. We found, further, that when we stimulated sympathetic nerves to smooth muscle elsewhere, *e. g.*, in the abdomen, we could produce the same effects on the denervated heart and on other denervated structures. Thus the submaxillary gland and the nictitating membrane could be rendered active by exciting the splanchnics after severance of the liver nerves and removal of the adrenal glands. The conclusion drawn from these experiments was that such excitation causes the affected cells to liberate a substance into the blood stream and that this substance, carried elsewhere in the body, may have effects similar to sympathetic impulses. It is worthy of emphasis that the phenomenon occurs under quite normal conditions and that no drug—analogous to physostigmin—is required to make it obvious. Previous investigators, who had found a sympathomimetic substance in salt solution which had been in contact with structures stimulated through sympathetic nerves, called it "sympathetic substance." In place of this cumbersome expression we suggested the name *sympathin.*

The most recent chapter in this story, first told last year, is concerned with the nature of sympathin. In many respects sympathin resembles adrenin. Like adrenin it causes, as we have seen, a faster heart beat, a rise of arterial blood pressure, an increased flow of

saliva (in the cat), and a contraction of the nictitating membrane. Furthermore, as Bacq[30] has shown, adequate liberation of sympathin may increase blood sugar, inhibit the rhythmic movements of the intestine, shorten the *retractor penis* muscle, contract the spleen, relax the cat's non-pregnant uterus and dilate the pupil. In all these respects sympathin seems to be indistinguishable from adrenin. And this testimony from similar biologic reactions is in accord with testimony from chemical studies. In applying a modified Viale test, sensitive to adrenin 1 to 30,000,000, Bacq[31] found the intensity of the color change greater, in the aqueous humor of the eye and in the fluids from a skin vesicle after the sympathetic nerves to the parts had been excited, than it was before. The color change, though not specific for adrenin, indicates that the chemical structure of adrenin and that of some substance produced by sympathetic impulses (sympathin) are alike. After all this evidence had accumulated we naturally inferred, as others also had inferred, that sympathin was simply adrenin produced locally in the responsive cell on the arrival of nerve impulses, as Elliott suggested 30 years ago. Last year, however, Rosenblueth and I[32] found that sympathin and adrenin are different.

The discovery came about in this way. We were looking for further resemblances between the two substances—adrenin and sympathin. Dale had shown, in 1906, that the drug ergotoxin blocks the influence of adrenin on vessels constricted by sympathetic impulses, while leaving unaffected vessels dilated by such impulses. After an appropriate injection of ergotoxin, therefore, adrenin, instead of causing a rise of blood pressure, causes a pure *fall*. Is the action of sympathin affected by ergotoxin in a similar manner? was the question we asked. We administered to an animal under anesthesia a proper amount of ergotoxin, proved that adrenin caused a fall of pressure, and thereupon stimulated the sympathetic fibers leading to the hind legs and the tail. To our great surprise the blood pressure, after an immediate slight fall, entered a prolonged rise; and hepatic nerve stimulation, such as Uridil and I had employed in 1921, produced a *pure rise*. Clearly sympathin and adrenin are not exactly the same. If they were, they would act the same.

The difference seemed to be expressed by an inability of sympathin to induce relaxation after ergotoxin. We then noted that in producing sympathin we had been stimulating regions (the liver and the tail) in which by sympathetic impulses we produced *contraction*. What would happen if, instead, we produced relaxation? We decided to try out that idea on different organs, contracted or relaxed by adrenin, and to avoid ergotoxin. To that end we selected as *indicators* the denervated nictitating membrane as an organ contracted by adrenin, and the denervated non-pregnant cat uterus as an organ relaxed by adrenin. As a *source* of what may be

called "contractile" sympathin we selected the liver. We found, to our great interest, that when the hepatic nerves were stimulated, the nictitating membrane contracted, but the uterus, though highly sensitive to adrenin, failed to relax. Recall that hepatic nerve stimulation, after ergotoxin, caused a pure rise of blood pressure, as if the sympathin which was given off had only a contractile effect. If the nerves on the duodenohepatic artery are stimulated, however, they produce two effects—*contraction* of smooth muscle in the blood vessels of the liver and duodenum and *relaxation* of smooth muscle in the duodenal wall. In these circumstances we found that not only does the nictitating membrane contract, but the uterus relaxes. Now if the nerves to the duodenum are severed and the same stimulus as before is applied to the nerves on the duodenohepatic artery, only contraction of the nictitating membrane results.

From these and accessory experiments Rosenblueth and I suggested that there are two kinds of sympathin—sympathin E, given off from smooth muscle which is excited to contract by sympathetic impulses, and sympathin I, from smooth muscle inhibited or relaxed by such impulses. Escaping from the cells of origin, sympathin E, borne by the circulating blood, is able to cause contraction in distant smooth-muscle organs which contract in response to sympathetic excitation; and sympathin I, analogously, affects smooth-muscle organs which relax.

The results just described have a direct bearing on the ideas expressed by Langley in 1905. Remember that he assumed that two different receptive substances, excitatory and inhibitory, exist in cells affected by adrenin, and that the different effects of that agent in different regions are due to the difference of these two substances. Researches by Rosenblueth[33] connect our results with Langley's ideas. Rosenblueth injected adrenin in gradually increased doses and found that the degrees of response of various viscera, when plotted, fell into a typical hyperbolic curve, the curve indicating chemical union. The inference was drawn that the adrenin, A, unites with a hypothetical substance, H, making AH, before it becomes effective. A similar hyperbolic curve resulted when maximal shocks were applied with increasing frequency to the sympathetic nerves which supply the same viscera. Again the evidence indicated that the mediator, M, set free in the cells by the nerve impulses, unites with a hypothetical substance, H, before acting. The experiments which led us to conclude that two kinds of sympathin exist, have led us to assume, further, that the hypothetical substance, H, must be separated into two distinct substances, E and I. Then M, the primary chemical mediator, when united with E, would become sympathin E; and when united with I, sympathin I. And ME and MI would have the same effects on remote smooth-muscle cells, which they enter from out-

side, as they have in the cells in which they originate. Thus Langley's insight appears to be substantiated by facts.

It is noteworthy that sympathin, the chemical representative of sympathetic impulses, is much more stable than acetylcholin, the representative of the parasympathetic impulses. Whereas the former can readily be shown not only to be present in circulating blood but to coöperate with adrenin, and to have widespread effects in the body, the demonstration of acetylcholin in the circulation is difficult and requires specially devised conditions to prolong its normally brief existence. This striking difference between the two mediating substances is quite in harmony with evidence as to the difference of neural organization of the sympathetic and the parasympathetic divisions of the autonomic system. The sympathetic neurons are organized for diffuse discharge of their impulses throughout the organism, to produce related adjustments of bodily processes—a provision favored by coöperation of sympathin and adrenin simultaneously set free in the blood stream and acting, therefore, diffusely. The parasympathetic neurons, on the other hand, are arranged for specific effects on separate organs—constriction of the pupil, for example, and slowing of the heart. These effects are quite unrelated. If acetylcholin were a persistent agent in the blood, it might bring about temporally related changes in biologically unrelated phenomena. Fortunately that result is avoided by the extreme instability of the mediator of parasympathetic impulses.

In following the records up to this point I have mentioned only the humoral agents manifested when the autonomic system acts upon cardiac and smooth muscle and on certain glands. The reason for that selection was that in those respects the historical sequence of ideas and evidence could be clearly traced, step by step, in a way that seemed to me interesting and possibly illuminating. Another similar movement, somewhat aside from this main current but in the same direction with it, has been the development of evidence that the chromatophores of both vertebrates and invertebrates are under chemical control. Time does not permit, on this occasion, even a brief report of the ingenious experiments which have led to that conclusion. In Parker's[34] little volume will be found an admirable and entertaining account of that aspect of recent progress.

At the outset I said that the story of our gradual understanding of the chemical mediation of nerve impulses would lead us to the point where we could look forward to new triumphs of physiologic investigation. That fair prospect lies in the direction of the nervous system. Certain characteristic features of reflexes include a failure of a single afferent impulse to evoke a response, whereas repeated impulses are effective; and also a continuation of the response for some time after the stimulus has ceased to act—the so-called "after

discharge." About 9 years ago Sherrington[35] suggested that a more or less persistent central excitatory state (or a central inhibitory state), without a refractory period and subject to summation, might explain these phenomena. It was assumed that repeated impulses could build up the state in a center until it became capable of discharging efferent impulses, or it could be built up to such a degree by rapidly repeated, strong stimulation that it would continue to discharge for some time before returning to the resting condition. Later Fulton[36] substituted "substance" for "state," and the concept of central excitatory or inhibitory *substance* was expounded, a concept at once related to the peripheral mediation of nerve impulses, with excitatory and inhibitory attachments, that we have been considering. Some quite recent researches have given support to the reasonableness of the idea that between the neurons of the nervous system, as well as between outlying autonomic neurons and their effector organs, chemical agents of transmission intervene.

Last year Kibjakow,[37] a Russian investigator, published important observations made on the perfused superior cervical sympathetic ganglion of a cat. While the salt solution was running through the bloodvessels of the ganglion, he stimulated the related cervical sympathetic strand, causing thereby, of course, contraction of the nictitating membrane. He found that the perfusate, when later passed through the blood vessels of the ganglion, had no effect if it came away before or after the stimulation; but if it came away during the stimulation it showed signs of having acquired a new property, for it now caused a contraction of the nictitating membrane. In short, some substance conveyed in the fluid had the same effects as the nerve impulses. Since Kibjakow's experiments were reported Feldberg and Gaddum,[38] working in Dale's laboratory, have brought forward evidence that in the transfer of nerve impulses from neuron to neuron in sympathetic ganglia, a chemical agent appears and that this agent is acetylcholin.

Meanwhile Rosenblueth[39] published a research in which he studied the effects on the heart of discharge from accelerator and inhibitor centers when these centers are affected by increasing frequencies of maximal stimuli applied to their afferent nerves, just as he had previously studied the effects on smooth muscle when stimulated through its nerves. The resulting changes in heart rate could be plotted in a rectangular hyperbola similar to that for smooth muscle —a resemblance indicating that the reflex output from the centers is directly proportional to the excitatory input. This linear relation between input and output could be explained without invoking chemical intervention in the conducting process. The *duration* of the output from the centers, however, is hard to account for in other terms than those of chemical mediation. As the frequency of the maximal efferent impulses was increased the persistence of

the reflex effects became longer and longer—indeed, in some instances not subsiding before a lapse of 10 minutes! When the peripheral nerves of the heart were stimulated, the recovery of the former rate was prompt. It is clear, therefore, that some change induced in the centers, no matter whether excitatory or inhibitory, persists for a long period and throughout the period continues the discharge of nerve impulses. The hypothesis that explains the results better than any other is that the central change is chemical in nature.

At this point one can let one's imagination play. It seems not improbable that a great new realm of physiologic research is opening before us, research which will disclose the mode of operation of the most mysterious part of the organism, the central nervous system. We may soon have proof of chemical mediation in central nervous processes, and know what the mediator is. As time goes on we may be able to tell in chemical terms why sometimes the processes are retarded, sometimes greatly accelerated. In the future we may be able to apply to the nervous system the ideas worked out on smooth muscle, and realize that the depression of manic-depressive state results from excess of inhibitory substance at some region in the brain, while the excitement means excess of the excitatory substance. But such dreams are only too easy. Cautious progress, step by step, is the safer mode of progress. And in the future, as in the past, carefully controlled experiments—experiments in which lower animals will be humanely employed—will be the most important means of advancing our knowledge.

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ON THE INHERITANCE OF DIABETES MELLITUS.

II. Further Analysis of Family Histories.

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The Necessity for a Correction in the Mendelian Expectation of Diabetes. A first analysis of the possible basis of the hereditary transmission of diabetes mellitus (Pincus and White[4,5]) dealt with the probability that a single recessive gene was the genetic factor concerned. The overwhelming proportion of traits ordinarily subjected to genetic analysis are identifiable at birth or shortly thereafter. Albinism, for example, is an immediately and easily observable condition, and the problem of its inheritance requires merely the examination of the proportions of albino and non-albino individuals in various types of matings, and the determination of the conformation of these ratios to any particular theory of the inheritance of albinism. Diabetes, on the other hand, is a condition which is definitely not identifiable immediately, but one which is manifested in different individuals at different ages. The ordinary age-incidence statistics indicate that certainly not until age 90 is

reached will every potential diabetic develop definite symptoms of the disease. Accordingly, if the analysis of the inheritance of diabetes were to be made completely similar to the analysis of the genetics of albinism, it would be necessary to examine families every member of which had lived to age 90 or beyond. In all the family histories that we have collected we have not found a single one that satisfies this condition. It became necessary, therefore, to construct a correction to the simple Mendelian expectation. This correction was calculated by assuming that every potential diabetic before developing the disease was subject to the ordinary chances of death, and then obtaining for every decade of life the percentage of potential diabetics actually developing the disease by applying the ordinary life-table expectancies to the best available statistics of diabetes incidences.

Material and Methods. It will be noted that we assumed that "ordinary" life table expectancies apply to diabetics before they develop the disease. When these expectancies taken in our previous analysis (Glover, U. S. registration area for 1910) were applied to the age-incidence data for diabetes collected by Joslin over the period 1898 to 1926, an estimate of the proportion of potential to identified diabetics was obtained for each decade of life. No attempt was made to justify the use of the 1910 life tables except by the statement that they must apply roughly to the incidence data collected over the stated period of years. Our population of diabetic families contained certain persons exposed to the chances of death existing during the 19th century, other persons exposed to the 1933 risks, and between these two extremes various persons exposed to the risks of intervening periods.

We have examined the questions of what sort of life tables might apply, and whether the application of any particular set of life expectancies is preferable or justifiable in obtaining the corrections, or whether the employment of any reasonable life table gives us the general result our Mendelian hypothesis would demand. The results indicate that as long as persons die in the rather regular manner indicated by the usual life table, and as long as diabetes develops with the usual frequencies per decade, the expectation of diabetes in diabetic families satisfies as well as can be expected the hypothesis that the development of diabetes is dependent on the transmission of a single recessive gene. We may note that the analysis which follows makes no pretense to great statistical refinement, chiefly because the limitations of the available data would make great refinement misleading and pretentious.

Our calculations of incidence are based upon Joslin's records taken on 9853 patients, from the years 1898 to 1933, inclusive. These data represent the most extensive series now available to us. They are usable only if they give a fairly accurate picture of the ordinary age incidence of diabetes. Fortunately they are derived from a practice which deals with diabetics of all ages, and is not concerned with diabetes in any particular age group, with the possible qualification that cases appearing in recent years *might* contain a slight excess of younger diabetics.

It happens that Joslin's data differ from the general statistics of diabetes incidence based upon mortality (Pincus, Joslin and White[6]). This is true even if the mortality statistics are corrected for the presumed duration of the disease. (Tables 1 and 2.) We, therefore, employ the Massachusetts data on deaths due to diabetes, and correcting them for duration (on the basis of the duration data given by Joslin[2]) we set up a second set of inci-

dence data differing markedly from Joslin's in order to ascertain the alteration in Mendelian expectations that would ensue. The Massachusetts data were collected over roughly the same period that Joslin's data were collected. It is necessary, in order to apply these data, to construct age specific rates of diabetes onset in a population having the same general age distribution as our diabetic families. A careful analysis of the mortality rates among the children of these families shows that the 1920 mortality rates apply with moderate accuracy. Accordingly we derive Tables 1 and 2, which present life tables based on mortality rates corresponding rather closely to those of 1920, but sufficiently modified to approximate the life expectations required by our observed population of children. We employ a smoothed life table rather than one that can be derived from our population of children chiefly because it is scarcely possible to adjust for the great excess of deaths due to diabetes in our data; but also in order to approximate with some reasonableness the presumed population from which our general onset data are derived. These tables are, therefore, only approximate, and the expectancies derived from them cannot be used for any exact tests of significance. None the less they are necessary for two purposes: (1) To ascertain the presumable number of genetically diabetic parents, and (2) to obtain a correction to our Mendelian probability of genetically diabetic individuals among the children.

Before proceeding to any analysis of the population of children it is necessary to determine the genetic nature of the matings that produced them. We designate a genetically diabetic individual by the symbol *mm*. Since each of the matings employed in our analysis produced at least 1 diabetic child, the possible parental combinations are: (1) $Mm \times Mm$, (2) $Mm \times mm$, (3) $mm \times mm$. Every diabetic parent we can classify at once as *mm*. But our incidence tables tell us that a number of potential diabetics will die before they exhibit symptoms of diabetes. The problem is to determine how many of such individuals exist among our parents, and, furthermore, how many of the living parents are potential diabetics. Since we know nothing of the matings which produced these parents we can only approximate this number. This is done by assuming that the observed numbers of diabetic parents represent a certain proportion of the total number of potential diabetics in the parental population. It happens that these parents are a particularly long-lived group of persons, so that the mortality rates of our incidence tables do not apply particularly well until the 7th decade is reached; and, since, according to Table 1, the 6th decade is the decade of maximum incidence, there is exceptional opportunity for diabetes onset among the parents. Even on the basis of the data of Table 2 (where the 7th decade is the decade of maximum incidence) the low early mortality rates should give us an exceptionally large number of recognized diabetics among the parents. Assuming then that the observed diabetic parents in each decade represent that proportion of the total number given by our incidence tables, we calculate on the basis of Table 1 (correcting for the presence of a small number of living parents) that there are in the parental population an average of about 63 potential male diabetics and 95 potential female diabetics, which leaves respectively 5 male parents and 7 female parents or a total of 12 potentially diabetic parents unidentified.* Similarly, on the basis of the data of Table 2 there are 175 potentially diabetic parents unidentified.

* The 4 diabetic male parents appearing in Decade 4 (Table 6) are taken as 7.12% (see Table 1, Column 4) of the total that were alive at the beginning of that decade. Therefore, 56 potential diabetics were alive at age 30. The total number of male parents identified is 58, or 2 more than expected. We go through the table of parents in a similar way, decade by decade, and so arrive at a rough estimate of missing *mm* parents.

TABLE 1.—LIFE TABLES FOR POTENTIAL DIABETICS ACCORDING TO JOSLIN'S INCIDENCE DATA.

Decade.	(1) No. identified (per 100 born alive).	(2) No. dying before identification (per 100 born alive).	(3) No. unidentified alive at beg. of decade.	(4) No. identified during decade as % of no. alive at beg.	(5) No. dying during decade as % of no. alive at beg.	(6) No. identified (per 100 born alive).	(7) No. dying before identification (per 100 born alive).	(8) No. unidentified alive at beg. of decade.	(9) No. identified during decade as % of no. alive at beg.	(10) No. dying during decade as % of no. alive at beg.
	♂ o_x	♂ d_x	♂ l_x	♂ $\frac{o_x}{l_x}$	♂ $\frac{d_x}{l_x}$	♀ o_x	♀ d_x	♀ l_x	♀ $\frac{o_x}{l_x}$	♀ $\frac{d_x}{l_x}$
1 . . .	1.76	12.67	100.00	1.76	12.67	1.42	10.58	100.00	1.42	10.58
2 . . .	2.91	2.93	85.57	3.39	3.42	2.25	2.06	88.00	2.57	2.35
3 . . .	4.04	3.85	79.73	5.06	4.82	2.19	4.35	83.69	2.64	5.24
4 . . .	5.98	4.68	71.84	8.32	6.51	4.28	5.11	77.15	5.54	6.53
5 . . .	11.91	4.99	61.18	19.44	8.16	11.91	5.00	67.76	17.57	7.30
6 . . .	15.90	5.50	44.28	35.88	12.42	20.81	5.69	50.85	40.89	11.19
7 . . .	11.69	5.12	22.88	51.01	22.32	13.64	4.86	24.35	55.95	19.90
8 . . .	3.57	2.22	6.07	58.33	36.36	3.46	2.04	5.85	58.67	34.69
9 . . .	0.12	0.16	0.28	37.50	62.50	0.17	0.18	0.35	38.46	46.15
Totals . .	57.88	42.12	...	...	...	60.13	39.87	...	...	...

TABLE 2.—LIFE TABLES FOR POTENTIAL DIABETICS ACCORDING TO MASSACHUSETTS MORTALITIES CORRECTED FOR DURATION.

Decade.	(1) No. identified (per 100 born alive).	(2) No. dying before identification (per 100 born alive).	(3) No. unidentified alive at beg. of decade.	(4) No. identified during decade as % of no. alive at beg.	(5) No. dying during decade as % of no. alive at beg.	(6) No. identified (per 100 born alive).	(7) No. dying before identification (per 100 born alive).	(8) No. unidentified alive at beg. of decade.	(9) No. identified during decade as % of no. alive at beg.	(10) No. dying during decade as % of no. alive at beg.
	♂ o_x	♂ d_x	♂ l_x	♂ $\frac{o_x}{l_x}$	♂ $\frac{d_x}{l_x}$	♀ o_x	♀ d_x	♀ l_x	♀ $\frac{o_x}{l_x}$	♀ $\frac{d_x}{l_x}$
1 . . .	1.18	11.58	100.00	1.18	11.58	0.83	9.62	100.00	0.83	9.62
2 . . .	1.72	3.10	87.42	1.97	3.55	1.22	2.49	89.55	1.36	2.78
3 . . .	2.35	3.28	82.42	2.85	3.98	1.48	3.80	85.84	1.72	4.43
4 . . .	5.35	4.77	76.79	6.97	6.21	2.85	5.22	80.56	3.54	6.48
5 . . .	5.23	5.25	66.67	7.84	7.87	6.49	5.28	72.49	8.95	7.28
6 . . .	9.98	6.91	56.19	17.76	12.30	11.60	6.64	60.72	19.10	10.94
7 . . .	10.03	9.00	39.30	25.52	22.90	11.67	8.81	42.48	27.47	20.74
8 . . .	7.04	8.88	20.27	34.73	43.81	8.20	9.05	22.00	37.27	41.14
9 . . .	1.23	3.12	4.35	28.28	71.72	1.46	3.29	4.75	30.74	69.26
Totals . .	44.11	55.89	...	...	...	45.80	54.20	...	...	...

Results. On the basis, then, of Joslin's incidence data we may consider practically all the matings of non-diabetic by non-diabetic as $Mm \times Mm$ and the matings of non-diabetic by diabetic as $Mm \times mm$. Distributing among the non-diabetic parents the 175 unidentified potential diabetic parents derived from the Massachusetts incidence tables, we arrive at 159 genetically *mm* parents in the non-diabetic by non-diabetic group and 16 genetically *mm* parents in the non-diabetic by diabetic group.

Considering now the children in these matings, we observe the age grouping (Table 3). The problem we must set ourselves is

TABLE 3.—TABULATION OF CHILDREN ACCORDING TO AGE IN THE VARIOUS MATINGS.

Decade.	Neither parent diabetic.						One parent diabetic.					
	Patients (diabetic).		Non-diabetic siblings.		Diabetic siblings.		Patients (diabetic).		Non-diabetic siblings.		Diabetic siblings.	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1 . .	36	26	148	143	1	2	1	2	30	25	1	1
2 . .	38	48	100	80	6	4	4	1	5	9	2	1
3 . .	27	28	144	129	1	1	6	8	19	28	2	1
4 . .	27	39	130	133	6	5	9	12	36	30	2	2
5 . .	44	83	147	191	10	5	13	23	44	59	4	6
6 . .	67	97	218	208	18	10	14	21	38	43	10	7
7 . .	43	64	150	156	5	13	2	8	30	24	1	4
8 . .	88	9	73	59	3	7	..	2	9	7	1	3
9 . .	..	..	5	7	1	..	..	..	..	2	..	..
Totals .	290*	394	1115	1106	51	47	49*	77	211	215	23	25

* The age at onset of diabetes of 1 patient was unknown.

this: What is the probability of identification of diabetics in the populations observed in these two types of matings? According to Tables 1 and 2 we can, in a *completed* population of potential diabetics subject to the mortalities of these tables, identify at most respectively 57.88% and 44.11% of the potential male diabetics born alive and 60.13% and 45.8% of the potential female diabetics born alive (Columns 1 and 6). The populations of children are, however, not completed since most of them are, in fact, still alive. We obtain an estimate of the proportions that should be identified, however, by the use of Columns 4 and 9 of these two tables. When this is carried through using Table 1, we determine that in the matings of (I) non-diabetic by non-diabetic 36.8% of the potential male diabetics born alive should be identified and 39.2% of the potential female diabetics. In the matings of (II) non-diabetic by diabetic the proportions are 38.7% of the males and 41.2% of the females. This gives us a mean probability of identification of 38% in matings (I) and 40% in matings (II). Similarly, employing the expectancies of Table 2 the mean probability of identification is 23% in (I) and 24% in (II). In Tables 4 and 5 we present the expectations derived by employing these probabilities. Thus in $Mm \times Mm$ families the simple Mendelian probability (p^1) is $\frac{1}{4}$ and the probability of identification as diabetic of mm individuals (p^{11}) is $\frac{38}{100}$ (on the basis of Table 1), giving us a probability of identified diabetics of $\frac{95}{1000}$ $\left(e.\,g.,\ \frac{1}{4} \times \frac{38}{100}\right)$. In order to correct for the fact that these families were observed because at least 1 child

TABLE 4.—THE EXPECTED AND OBSERVED NUMBER OF DIABETICS IN MATINGS OF 2 NON-DIABETIC PATIENTS.

Family size by No. of children.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Totals.
No. of patients	62	104	118	113	98	67	45	31	20	16	4	4	1	2	685
Total No. of children	62	208	354	452	490	402	315	248	180	160	44	48	13	28	3004
No. of diabetic children	62	116	134	127	111	85	53	38	28	20	4	5	1	33	783
No. of diabetic children (1)	62	109.18	129.95	130.27	118.38	84.66	58.09	42.80	28.72	24.06	6.27	6.53	1.70	3.48	806.09
expected* (2)	62	107.83	126.76	125.85	112.95	80.11	55.76	39.60	26.55	21.87	5.68	5.86	1.39	2.86	775.07
No. of diabetic siblings (1)	0	5.18	11.95	15.27	20.38	17.66	13.09	11.80	8.72	8.06	2.27	2.53	0.70	1.48	121.09
expected* (2)	0	3.83	8.76	12.85	14.95	13.11	10.76	8.60	6.55	5.87	1.68	1.86	0.39	0.86	90.07
No. of diabetic siblings observed	0	8	16	14	13	18	8	7	8	4	0	1	0	1	98

* The numbers in parentheses refer to expectancies derived from Tables 1 and 2 respectively.

TABLE 5.—THE EXPECTED AND OBSERVED NUMBER OF DIABETICS IN MATINGS OF 1 DIABETIC BY A NON-DIABETIC.

Family size by No. of children.	1	2	3	4	5	6	7	8	9	10	11	12	Totals.
No. of patients	7	23	30	19	12	10	14	9	8	4	0	1	127
No. of children	7	46	60	76	60	60	98	72	72	40	0	12	603
No. of diabetic children	7	26	23	28	21	17	20	18	10	4	0	1	175
No. of diabetic children expected (1)	7	25.55	24.59	25.74	71.84	16.27	24.78	22.07	16.63	8.96	0	2.58	192.01
(2)	7	24.69	23.06	23.27	15.93	13.88	20.99	14.15	13.34	7.59	0	1.77	165.67
No. of diabetic siblings expected (1)	0	2.55	4.59	6.74	5.84	6.27	10.78	13.07	8.63	4.96	0	1.58	63.43
(2)	0	1.69	3.06	4.27	3.93	3.88	6.99	5.15	5.34	3.59	0	0.77	38.67
No. of diabetic siblings observed	0	3	3	9	9	7	6	9	2	0	0	0	48

(*e. g.*, the patient) was present, we employ the formula $\frac{p}{1-(q)^n}$ to obtain our final probability, where p is the probability of identifying as diabetic an *mm* individual, q the probability that identification will not be made, and n the number of children in the family. Thus in families of 3 children the final probability is $\frac{0.095}{1-(0.905)^3}$ or 0.3671 (*e. g.*, 36.71% of the children in families of 3 should be identified as diabetic). Strictly, we should determine the probability of identification (p^{11}) separately for each group of families of the various sizes. We have not done this because separate life tables for the various-sized families are not justified by the meager data then assembled, and because our probability tables for identification (Tables 1 and 2) are at best approximations. If we did set up the separate p^{11} for these matings according to family size some of the discrepancies in Tables 4 and 5 would disappear; the p^{11} for families of small size would be higher than 0.38 or 0.23 in $Mm \times Mm$ matings, since these families contain less infantile deaths and generally longer-lived persons than the families of larger size where the large size is due in part to the listing of all children dying in infancy. This would increase the expectation of diabetic siblings in families of small size and decrease it in families of large size. The actual differences are, however, relatively small and the gross expectations arrived at represent good approximations.

The totals* requiring closest comparison are obviously those for siblings, since the patients serve merely to bring a given family into our tables. It is at once obvious that on Joslin's incidence data we have a deficiency of diabetic siblings, and on the Massachusetts data we have an excess with a somewhat closer agreement when the general incidence data are employed. This implies that Joslin's onset tables contain relatively too many younger persons, and we noted that this may be true since his practice has been largely consultative and would tend to include more severe diabetics (*e. g.*, younger persons).

Discussion. It is obvious that a fair approximation to Mendelian expectations is had with the use of two definitely different estimates of diabetes onset incidences. If we regard Joslin's data as standard, then there is a deficiency of diabetics among the children; if the Massachusetts data are used as standard, there is a slight excess of diabetic children. That the derived expectations of diabetics differ less than one would superficially expect is due to the fact that on Joslin's data the lesser number of missing *mm* parents increases the Mendelian probability (p^1) only slightly, whereas the Massa-

* We have also several matings of conjugal diabetics (*mm* × *mm*) in these series. On the basis of Tables 1 and 2, 12.83 and 7.86 diabetics are expected among the 40 siblings; 8 diabetic siblings were observed.

chusetts tables require an increase in p^1 due to a considerable number of missing *mm* parents, but a decrease in the probability of identification among the children (p^{11}). Clearly neither the Joslin data nor the Massachusetts data can be taken as completely adequate representations of the age distribution of diabetes onset. They are necessarily approximations. In order to calculate completely accurate probabilities of identification we should have the full distribution of diabetics according to age in a large population with exact mortality rates for that population. The most complete statistics of diabetes incidence are the registrations of death due to diabetes. But we are scarcely justified in employing the diabetes mortality statistics for the construction of life tables for potential diabetics, since it is highly questionable to assume that diabetics are subject to ordinary chances of death before they *die* of diabetes. If diabetes were lethal at onset we might make such an assumption, but the extent to which diabetics are likely to die of all other causes while they are actively diabetic is unknown.

It is, therefore, notable that with the data at hand we do arrive at results indicating the consistency of our observations with a Mendelian hypothesis.

Diabetes in Non-diabetic Families. All the foregoing analyses may be objected to on the grounds that in any group of families selected at random diabetes incidence may follow the same course. We have previously presented data comparing a diabetic with a control population, and found diabetes incidence in the two to differ significantly. Our comparisons were made employing the χ^2 method. Because of the rather scant data, we employed in certain decades calculated expectancies of less than 5, and this is open to certain theoretical objections. Since our previous publication our control population has been enlarged somewhat and we are able to make more reliable comparisons. Our control population was assembled by questioning a group of non-diabetic individuals about the incidence of diabetes in their families. (Table 6.) The total incidence of diabetics among the siblings and parents of our diabetic population is 6.7%, while in the control population it is 1.23%. This difference is statistically significant, but since the incidence per decade is the obviously fairest basis of comparison we have presented the data by decades. When the χ^2 method is employed to test the independence of the two groups we combine the data for Decades 1 and 2 and 3, 4 and 5, and 8 and 9, in order to arrive at expectancies greater than 5. The value of χ^2 arrived at for the 5 groupings employed is 56.996 and this gives a value of $P > 0.000001$. In short, the chances are less than 1 in 1,000,000 that the difference between these two populations is not significant. The incidence of 1.23% that we obtain for our control population may seem rather low, but in view of the fact that it is a comparatively young popula-

tion, this incidence is understandable. We have, if anything, selected in our control group for higher incidence, since the controls were obtained by questioning 1 member of a family who was not diabetic. Obviously if diabetes occurred purely at random these controls were selected for greater than normal incidence and the diabetic group for less than normal incidence. The highest estimates of diabetes incidence seldom exceed 2.5%, and the difference between 1.5% and 6.7% is, on the basis of the numbers in our diabetic population, decidedly significant. In fact, the general incidence of diabetes would have to be a minimum of about 6% in a similar age grouping to be less than significantly different from the incidence in our diabetic population.

TABLE 6.—A COMPARISON OF DIABETES INCIDENCE IN A CONTROL AND IN A "DIABETIC" POPULATION.

Decade.	Diabetic population.				Control population.			
	Total siblings.	Diabetic siblings.	Total parents.	Diabetic parents.	Total siblings.	Diabetic siblings.	Total parents.	Diabetic parents.
1 . . .	355	5	...	...	119	0	...	...
2 . . .	208	13	...	...	100	1	...	...
3 . . .	315	5	27	...	136	0	7	0
4 . . .	352	16	171	7	134	1	25	0
5 . . .	476	28	228	16	140	0	69	0
6 . . .	560	48	277	36	114	0	96	1
7 . . .	388	23	358	55	75	3	99	4
8 . . .	166	15	330	27	35	1	87	4
9+ . .	15	1	229	5	9	0	51	1
Totals .	2835	154	1620*	146	862	6	434	10

* 24 parents whose ages were unknown have been omitted from this table.

Secondary Factors in the Production of Diabetes. We may indicate briefly what the significance of our findings is for the etiology of diabetes mellitus. If our data be taken to indicate that the presence of a recessive gene (in double dose, *i. e., mm*) is necessary for the expression of diabetes, then it is at once obvious that the problem of etiology is in one degree simplified. For the question that remains to be answered is: Given the proper genic constitution, what determines that it shall be expressed as diabetes? One or several secondary factors may be involved, but they are factors which appear in a particular manner, as the incidence-age relations indicate. The fact that we must invoke such secondary factors in no way vitiates the postulation of a primary genic cause. No genes can operate *in vacuo*, and every case of genic action is attained only with the coöperation of other agencies. These may be environmental or internal. The data presented in this paper give but meager clues as to the secondary factors. If more delicate indices of the action of the presumed gene for diabetes were available, perhaps some more definite conclusions could be drawn.

It is perhaps pertinent to indicate that modern research indicates the possibility of the action of two factors in the production of diabetes mellitus. These are the failure of the pancreas to produce the normal quota of insulin and the production of a diabetogenic hormone by the anterior lobe of the pituitary gland (Evans,[1] and Marine and Baumann[3]). It is known also that an endocrine function may be definitely controlled by a Mendelian recessive, *e. g.*, the marked impairment of pituitary function in dwarf mice (Snell,[8] Smith and MacDowell[7]). In subsequent papers we may be able to consider more specifically the rôle played by the presumed gene for diabetes in relation to endocrine factors underlying manifestations of diabetes.

Summary. Among the parents and siblings of a group of diabetic patients the reported incidence of diabetics is 300 in a total of 4434 individuals (6.7%), whereas only 16 diabetics were reported in a total of 1296 parents and siblings of a group of non-diabetic patients (1.23%). The difference between the percentages observed is statistically significant. When the assumption is made that diabetes develops in individuals homozygous for a recessive gene (*i. e.*, in *mm* individuals), it can be demonstrated that the ratios of diabetic to non-diabetic individuals among the siblings of the diabetic patients conform with the consequent expectations, provided we assume that potential diabetics before they develop the disease are subject to the ordinary chances of death. Employing differing incidence data causes little variation in our Mendelian expectations. This is taken to indicate that as long as diabetes occurs in the fairly regular manner indicated by ordinary incidence tables, and as long as the chances of death indicated by the ordinary life tables apply, Mendelian expectations will be satisfied. It is, therefore, highly probable that the development of diabetes mellitus depends primarily upon the transmission of a single recessive gene. But the ordinary age-incidence relations indicate the operation of one or more secondary factors. Our data give no accurate clue to the nature of these secondary factors.

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NON-OPERATIVE VERSUS OPERATIVE MEASURES IN THE TREATMENT OF PULMONARY TUBERCULOSIS.

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The forces organized against tuberculosis today are pressing forward in three columns. The physicians are making a frontal attack, while the public health officials and surgeons are holding the right and left wings and pressing rapidly toward the center, where all forces, united, hope to cause a complete rout of the enemy.

At the outset of this discussion I wish to make plain that there is no antagonism between non-operative and operative measures in the treatment of tuberculosis. There is a vast difference in opinion as to when the one or the other should be employed, but such antagonisms as exist are between partisan advocates of the one or the other method. In this paper I wish to discuss the curability of tuberculosis and attempt to point out the manner in which healing is accomplished. I wish further to point out the factors which favor and those which prevent such an accomplishment, and to show how treatment must be suited to each case and further show that the correct treatment is conservative whether it be operative or non-operative.

I wish further to make plain that the particular measure which will be adopted will depend very much upon the opinion which the physician holds regarding the curability of tuberculosis, on the one hand, and its infectiousness both as far as forming metastases in the host and its danger of infecting others is concerned, on the other. He who has great confidence in its curability will be slower in interfering, while he who is imbued with the great danger of its spreading and forming new metastases, likewise he who is imbued with the great danger of infecting others, will interfere more quickly.

If patients could all be treated in an ideal environment by physicians who not only understand tuberculosis but who possess a mental attitude adapted to the treatment of chronic illness, and if the patients were so desirous of getting well that they would rigidly adhere to the necessary regimen, then the cure of early tuberculosis, like that of other infectious diseases, would be largely a matter

of natural and specific defense, and only complicating conditions would require a deviation from the well-established hygienic, dietetic, open air, rest regimen.

But such is not the case. Patients with various personalities which determine the degree of coöperation or lack of coöperation which they will give, with various domestic, social and economic problems to face, must be treated in various environments by physicians who have different conceptions of tuberculosis and personalities which endow them with different degrees of fitness for carrying out the treatment of such a chronic disease. These variants influence the success to be attained as much as the character of the treatment which is instituted to cope with the disease *per se*. Therefore, we cannot discuss the treatment of tuberculosis from a purely scientific standpoint, but must include its psychologic, social, domestic and economic aspects.

Therefore, a favorable result obtained by operative measures does not necessarily mean that it could not have been attained by non-operative measures, nor does one attained by non-operative measures mean that it could not also have been attained by operative measures. The point at issue is, which method best conserves the interest of the patient? and this can be determined only after taking into consideration and carefully weighing the dangers that may come to the patient by not using some operative measure and comparing them with any injury that may follow the employment of operative procedure.

Development of the Modern Methods of Therapy. For centuries, physicians were called only to treat patients suffering from what we now look upon as far-advanced tuberculosis. There was no organized program of treatment based on a knowledge of the disease, nor was there any accurately recorded experience on which to base opinions. Tuberculosis was not recognized as coming under public health control. It was not even classed among the reportable diseases. It was simply looked upon as an unpreventable and hopeless malady.

At the beginning of this century the entire picture changed. There was a steadily growing belief that tuberculosis could be cured and, further, that it probably could be prevented. A group of leaders with an increasing army of followers began to act upon this belief. A campaign of education ensued which was prosecuted with such zeal as had never before been witnessed in connection with any disease. Medical societies gave tuberculosis an important place on their program; public addresses were given; pamphlets were distributed; and laws were enacted to provide the measures necessary to prevent and the facilities necessary to cure the disease.

For the first time in history the medical profession began to take a real vital interest in tuberculosis. The result, the reduction

of tuberculosis to the sixth rank as cause of death, and the reduction of infection to one-half of its former amount, is one of the truly great medical triumphs. In the space of time marked by less than one-half of a generation we have so changed our attitude toward the disease, and so successfully devised methods for its prevention and cure, that we now feel that it is well on the way to be conquered or at least to be reduced to a position of importance comparable to that of other serious diseases.

As long as tuberculosis exists, however, it will be a disease of special importance, because of the fact that its prevalence is so much greater during the productive period of life than is that of most other serious diseases and, further, because of its chronicity and its slowness in healing.

Public health agencies are now spending their energies in the prevention of tuberculosis, and clinicians are devising methods for meeting the problems which arise in its treatment. Even the more serious types of the disease, those which were entirely beyond hope but a short time ago, are now being successfully treated. That we are able to relieve patients suffering from far-advanced lesions must not blind us to the most important fact that has been brought out by a quarter century of experience in the intensive treatment of tuberculosis, *viz.*, that early lesions are the most easily cured, and that they leave the patient in the most satisfactory state of health and most capable of carrying on his life's work. My experience leads me to state that it is practical rather than Utopian to believe that operative measures are only justifiable until such time as we are able to make early diagnoses and institute adequate treatment as soon as diagnoses are made.

In order to appreciate what each individual measure contributes to cure, it is necessary to have a fairly accurate understanding of the fact that tuberculosis is a bacteriologic disease which produces pathologic and immunologic responses which in turn alter anatomic structures and physiologic reactions. Some of these changes in structure and function are favorable while others are unfavorable. It is the duty of the physician, as far as he can, to recognize and promote the former and to prevent the latter.

Cure of Tuberculosis—An Immunity Reaction. The important factor in the cure of all infectious diseases is immunity. This is particularly evident in diseases of short duration, such as diphtheria and tetanus, in which the toxins are the lethal agents and the immunity is all but absolute; for these can be cured by the administration of immune bodies artificially produced. It is also readily understood in such diseases as typhoid in which protective inoculation of killed bacteria will immunize, or smallpox, in which an artificial vaccination will produce a miniature disease and protect the host from future disease. In tuberculosis, on the other hand, we have a disease, chronic in nature, which produces an immunity,

but one more difficult to understand. A miniature disease caused by a small number of bacilli will produce, at least for a time, a relative immunity against future inoculations, but is not able to grant a full immunity. Protection may also be granted by dead bacilli similar to that produced in typhoid vaccination, but again only relative and not so high as that given by a real infection caused by living bacilli.

Bacilli and the toxic substances produced by them are responsible both for the production of a relative increase in resistance to further inoculations and for injury and destruction of tissues. We have experimental evidence showing that inoculation of both living and dead bacilli will produce a relative degree of protection against new infection, and we have clinical observations which prove that the protective mechanism which is set going by natural inoculations of bacilli and bacillary products is effective in lessening the seriousness of later inoculations and in healing the disease.

In the natural healing of tuberculosis we rely on the patient's own body reactions to bring about healing, the same as in all other infectious diseases for which we do not have specific remedies. This protective mechanism differs with different individuals, both as to its efficiency and as to the time required for its development; but it is slow in all cases. This fact furnishes one of the chief causes of failure.

Tuberculous patients do not die because the disease is incurable, but because it is not cured. There is a time when nearly every patient suffering from tuberculosis has it within his power to attain a cure. That he does not do so is due to the fact that for one or another reason the disease is not brought under treatment at this favorable time, or that the kind of treatment is not suited to the condition at hand; or is not properly applied. We assume that healing is primarily a physiologic process, and that its accomplishment depends upon the establishment of a much higher degree of immunity than was necessary successfully to overcome the minor lesions of early infection.

We cannot describe categorically the factors which make for immunity, nor can we assign to each its particular part in bringing about healing, but we have learned that a good physiologic balance is a great asset. We have learned that rest is the most important single factor in maintaining such a balance during the stage of active disease. It produces its favorable effects in many ways. It lessens the energy requirements of the body at a time when the demands of increased energy cannot be easily supplied. It calls for a minimum of circulatory activity in the body and so in the lungs, and calls for a minimum of respiratory effort, thus putting the diseased areas at relative rest. This reduces the danger of metastases occurring and minimizes the escape of toxins from the foci, thus relieving

the patient of avoidable toxic symptoms. It reduces the body's food requirements to a minimum and permits of storing of any excess of energy for supplying future demands.

Rest of mind is as essential as rest of the body, so the development of a proper mental attitude is important. It can thus be seen that the control of the patient is necessary to guarantee to him a physical and mental rest. No matter what other measures are used in treatment, mental and physical rest should be maintained during the period when the disease is active.

If a carefully devised program, suited to the patient's particular requirements, is carried out sufficiently long, it will assure success in nearly all of those cases in which healing depends alone upon the resistance of the patient. In other words, a well-balanced physiologic state is sufficient to produce the cure in nearly every case at this favorable time.

I wish to emphasize this fact, because in our enthusiasm for operative methods we are prone to forget that if the disease were treated early, the conditions which require operation would be rarely met. Our slogan should be "early diagnosis and immediate, adequate treatment." In what instances are non-operative measures insufficient? This is the question to be considered.

The clinician may have his faith in the ability of the patient to cure his own disease greatly increased by patiently treating those who seem to offer little hope of cure unless the lung may be compressed by pneumothorax, or the tissues be relaxed by phrenic evulsion, and in whom attempts at the former have been unavailing and the institution of the latter has failed to cause elevation of the diaphragm, or by patiently treating certain extensive bilateral lesions which are not suitable for operation. In such cases it is not a rare thing to see the usual sanatorium regimen followed by healing.

I have formed the opinion from treating several thousand patients suffering from advanced and far-advanced tuberculosis that, if non-operative treatment is followed with sufficient detail and continued sufficiently long, most patients in whom we can establish and maintain a resistance sufficiently high to prevent extensive caseation with necrosis and serious new metastases from forming have an excellent chance of ultimately bringing their disease to a state of quiescence, and that, unless cavities which are too large or cavities possessed of dense walls, or mechanical conditions which prevent adequate compensation from taking place are present, they may go on to an eventual healing. It is the patients in whom metastases continue to take place, in whom destructive lesions are uncontrolled, or in whom mechanical factors interfere, that cannot heal readily.

The Mechanical Factors Which Interfere With Healing. As the disease progresses, however, there are certain factors which enter

into the picture that make healing difficult, sometimes even impossible, no matter how high resistance may be raised. These factors are largely of a mechanical nature.

The therapeutics of tuberculosis cannot be understood without taking these mechanical problems into consideration, for they really are the most important factors in separating tuberculosis into operative and non-operative. Too often, to the therapist, the cure of tuberculosis means some one particular thing—a hygienic regimen with rest and control as the chief factors, tuberculin, heliotherapy, pneumothorax, a phrenic evulsion or a thoracoplasty. Such an attitude toward cure is not rational and does not take into consideration the best conception of tuberculosis or the best interests of the patient.

The lungs are confined within the thoracic cage and are in close contact with rigid bony structures on all sides except at the base, where they are confined by the diaphragm. In tuberculosis a shrinking of the pulmonary volume takes place, whether as a result of destruction of tissue or by the replacement of elastic tissue by fibrosis, or by the reduction of the volume by exudation and atelectasis.

On the principle that Nature abhors a vacuum, the total volume of pulmonary tissue always must approach the amount necessary to fill the thoracic cage. When the volume of pulmonary tissue is reduced it can be compensated in only one of two ways: the structures which confine the lungs must contract and make the thoracic cage smaller, or the lungs themselves must compensatorily enlarge. These two processes go hand in hand as tuberculosis advances.

During the early stages of the disease the reduction in lung volume is of comparatively slight importance and usually is readily compensated by an emphysema of the uninvolved or less involved lung tissue. Later, too, it may be compensated, but with greater difficulty, and, finally, not at all. As soon as the stage is reached in which compensation is not readily made, healing is interfered with, and no matter how stable the patient's physiologic equilibrium or how competent his immunity, healing can go forward only with difficulty.

The mechanical conditions which particularly interfere with compensation are pleural adhesions, fixation of the mediastinum, adhesions and fixation of the diaphragm, widespread fibrosis, the emphysema which has developed prior to the time of the destructive lesion and rigid thorax.

The manner in which pleural adhesions interfere with healing may be studied in cases of bilateral apical tuberculosis, in which an apical, pleural cap is found on both sides. The tissues are rigidly fixed in an area as extensive as the adhesions. Contraction of the pulmonary tissues which accompanies the disease makes traction on the unyielding pleural adhesions. Since they cannot give way,

whatever compensating change occurs must take place from below, and, since the diaphragm is a muscle with strong contracting power, the compensation really must occur largely by the enlargement of the air cells, causing an emphysematous condition in that portion of the pulmonary tissue which is not involved in the tuberculosis. The seriousness of the interference which is caused by adhesions in double apical tuberculosis must be evident to any one who will note the extent of the shifting of the upper mediastinum which is at times necessary in order to compensate for the contraction which follows healing of unilateral lesions which involve the upper portion of the lung. The tension to which these tissues would be subjected were the mediastinum fixed is evident.

Again, the interference with healing which is caused by pleural adhesions is shown when an extensive one-sided adhesive pleuritis exists over a lung which is the seat of a severe lesion of either the exudative or the proliferative type. If a fixed mediastinum is also present, healing may take place, but is rendered very difficult without some operative measure which will aid in adjusting the intrathoracic space to the lung volume. If the adhesions do not involve the entire pleura, a partial pneumothorax may be of value, or a phrenicectomy may afford a considerable degree of aid. If a cavity of any considerable size is present, and particularly if it is situated in the midst of fibrous tissue and possessed of a thick wall, healing is rendered very doubtful, except as a result of operative assistance. Under these circumstances thoracoplasty may become practically our only hope.

The Characteristics of Proliferative and Exudative Lesions Which Modify Treatment. While the curability of tuberculosis depends upon the extent, age and activity of the lesion, it again depends upon whether it is predominantly proliferative or predominantly exudative. That there is a difference in exudative and proliferative tuberculosis has long been known, and recently we have begun to understand certain of the fundamental causes of this difference. The fact of this difference must be considered in applying therapeutic measures.

Predominantly proliferative tuberculosis has long been recognized as a comparatively benign process, one which primarily makes for fibrosis with chronicity rather than for acuteness with destruction. It has long been assumed that it is caused by relatively few and mildly virulent bacilli, and that the predominant reaction of the tissues is that of cellular proliferation rather than exudation and destruction.

Now that pure fractions of the bacillus have been given to us with which to work, it has been found experimentally that bacillary lipoids produce fixed-cell proliferation and tubercle formation, with little toxemia or exudative reaction, while bacillary protein causes exudation and destruction, and the polysaccharid seems to be the

chief toxic element. Sabin, using a phospholipin and injecting it into the peritoneal cavity of animals, has been able to produce huge proliferative masses of tissue, so we now explain proliferative tuberculosis as being predominantly a reaction of the body to the lipoids of the bacillus, to the bacillus as a foreign body, in contradistinction to its reaction to the bacillary proteins and polysaccharids or the bacillus as a living immunizing substance.

It is also characteristic of predominantly proliferative tuberculosis that it extends in spite of its mildness. It seems to fail in calling out the immunizing mechanism which raises the patient's specific resistance, prevents the ready passage of bacilli through the tissues and increases the body's power to destroy them. Sooner or later, however, exudative phenomena appear, destruction of tissue takes place, symptoms of intoxication supervene and the process becomes a combination of proliferative, exudative and often destructive characteristics with increased acuteness, and, at the same time, with evidence of a heightened immunity. Unfortunately the immunity makes its appearance, as a rule, after extensive fibrosis has taken place, and the tissues are harboring widespread infection.

Predominantly proliferative tuberculosis, because of its mild nature, bears a reputation for ready healing which it does not deserve. In my experience a proliferative lesion produces milder reactions, extends more slowly, but often is far more difficult to heal than a preponderantly exudative lesion of similar extent. And when it does heal it leaves the lung tissue replaced by extensive scar, while the exudative lesion heals largely by resolution, leaving only a minimum amount of scar.

Predominantly exudative tuberculosis is a more acute process. We assume that it is caused by larger quantities of more virulent bacilli than those which are responsible for the preponderantly proliferative lesions, and that through their growth, rapid multiplication and destruction, large quantities of bacillary lipoids, protein and polysaccharids are set free in the tissues. The exudative response is called out as the body's reaction to the protein fraction, which is the same fraction that stimulates the patient's immunity mechanism. The toxicity, however, is probably largely due to the polysaccharid. New tissue formation takes place as a healing measure, but it is limited in extent and secondary to resolution of the exudate. Extensions do not take place gradually, as in the predominantly proliferative type of disease, but more precipitately and result in more acute reactions on the part of the patient, a greater toxicity and a more efficient immunity.

The symptoms of acuteness result from the rapid destruction of bacilli and the liberation of bacillary products, particularly the polysaccharids and proteins.

Pulmonary Lesions Which May Heal By the Hygienic Rest Regimen Alone and Those Which Require Operative Assistance. From the purely scientific standpoint in which the curability of tuberculosis

alone is considered, the following types will heal fairly regularly without operative assistance:

1. Early limited lesions of either the proliferative or exudative type.
2. Proliferative lesions more extensive than those mentioned under Group 1, involving one or both lungs, provided they have not taken on extensive metastases and destructive processes with multiple cavitation.
(*a*) Small cavities may usually be expected to heal, but the healing of large ones, especially if multiple, is more doubtful without operative aid.
(*b*) Whether or not such lesions will heal depends much upon the extent of injury which has been done to the lung tissue and the ease with which the necessary compensatory changes between lung volume and intrathoracic space may be made.
3. Exudative lesions more extensive than those mentioned in Group 1, with or without cavity, provided the non-infected lung tissue can take on the required emphysematous changes and the mediastinum is free to shift in case it is required by the compensation which must be made, and provided further that other limiting structures are able to accommodate themselves to the reduced lung volume.
Early cavity in exudative tuberculosis is not a contraindication to healing unless it is held open by pleural adhesions and a fixed mediastinum, or so located that it cannot close.
4. Exudative lesions which are accompanied by extensive atelectasis will usually heal even though they may be accompanied by high temperature which requires several months to reach normal.

From the purely scientific standpoint, this leaves practically no early cases that regularly require operative assistance, but as the disease advances there are several types of lesion which cannot be depended upon to heal without operative aid, some of which are the following:

5. Comparatively small lesions with a cavity which is held open by pleural adhesions, and is prevented from closing because the unaffected lung tissue is not able to make the necessary compensatory changes, such as apical or subapical cavities covered by a pleural cap, and especially when the upper mediastinum is fixed.
6. Any active lesion which continues to form metastases unduly long in spite of carefully followed non-operative treatment.
7. Lesions in which a destructive process is seriously threatening cavity formation; in fact, should cavitation threaten during the course of chronic tuberculosis, it should probably always be prevented by collapse if possible.
8. Any lesion which is prevented from healing by mechanical hindrances. This will include:
(*a*) Small cavities situated so that the walls cannot collapse as in the apex covered by a pleural cap; small cavities in dense scar tissue situated in any part of the lung; and those near the hilum or diaphragm.
(*b*) Extensive infiltration, with or without cavity, in which the tissues are put on marked tension, and in which compensation necessary to healing cannot be readily made.
(*c*) Large cavities with thick fibrous walls.
(*d*) Cavities in a much contracted lung, with displaced mediastinum, in which further compensation cannot be made.

In my experience this grouping roughly separates the cases which may be expected to heal by non-operative measures from those which require operative assistance. It does not, however, repre-

sent the manner in which tuberculous patients are generally treated, because operative measures are so frequently found necessary to meet the exigencies under which treatment is carried out. Not only are the Groups 5, 6, 7 and 8 recognized as requiring operative aid, but some of Group 1, many of Groups 2 and 3 and practically all of Group 4 are usually treated by pneumothorax or phrenicectomy or both.

TUBERCULOSIS CASE-FINDING.

FIVE YEARS' EXPERIENCE WITH FLUOROSCOPY.

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IT has been shown definitely and frequently that pulmonary tuberculosis exists in many cases without abnormal physical signs and without suggestive symptoms. Therefore, in this discussion it will be taken for granted that, at the present time, the most effective and most secure way of making an early and definite diagnosis is by the use of the stereoscopic Roentgen ray film. This is the ideal method and the more frequently and repeatedly it is utilized, the more effective it becomes. It has, however, the disadvantage of expense, which, in many instances, is a decided drawback. Certainly this is apt to be true where large numbers of supposedly healthy people are to be examined; routine roentgenograms may be so expensive as to be prohibitive. If all, then, cannot be Roentgen rayed, the question arises how to select those cases which should have a Roentgen ray. Some or all of the following may be used as a basis for selection: (1) Physical examination; (2) history of suggestive symptoms or of contact with tuberculosis; (3) tuberculin reaction; (4) paper films; (5) fluoroscopic examinations.

The first method (physical examination) can be dismissed as being grossly inaccurate as a selective measure. This has been pointed out repeatedly.[1-8, 15] We do not wish to imply that physical examination of the chest should be omitted, but we emphasize that a negative physical examination does not rule out the presence of tuberculosis. On the other hand, the only reliable physical sign is the presence of râles persisting after cough, usually in the upper part of the chest. If these are present, the diagnosis of tuberculosis is to be strongly considered; if they are absent, tuberculosis may still be present in advanced degree. Other signs—cogwheel breathing, slight variations in percussion note and in intensity of breath sounds—are solely of academic interest; they have no practical value in establishing the diagnosis of tuberculosis.

The second method (history-taking) is of great assistance. All cases with a history of pleurisy, hemoptysis or cough of unusual duration should be Roentgen rayed. However, there are innumerable cases of early tuberculosis which do not present characteristic symptoms, but rather vague, ill-defined complaints (as lassitude, irritability, abdominal discomfort, menstrual variations, etc.), none of which seem related to disease of the respiratory system. Insistence that such a patient have a Roentgen ray of his chest is wise, but it is often difficult to accomplish. Moreover, there are many individuals with early (or advanced) tuberculosis in whom symptoms of any sort are either entirely absent or so slight that they escape attention[9,10]—the "Tuberculosis Unappercepta" of the German writers. "It is probable that every actual case of tuberculosis is preceded by such a phase, during which the fate of the patient is already, in many cases, decided to his disadvantage, unless his infection be discovered early through Roentgen ray examination."[11]

We have, for five years, observed a group similar to this (*i. e.*, positive Roentgen ray findings—absence of physical signs and symptoms) and have seen the disease progress in some instances to cavitation with an absence of signs and symptoms.[12] In our experience, early cases with no definite signs or characteristic symptoms far outnumber those cases presenting suggestive symptoms. We feel, therefore, that a selection for Roentgen ray based on symptoms will fail to include a large number of clinically significant cases.

The remaining case-finding methods are based upon laboratory procedures. The tuberculin reaction is of considerable value, more particularly in schoolchildren. As a basis of selection among adults, it is of less value because the number of positive reactors is so high.

The paper films, recently introduced as an economic method of examining large groups quickly, may prove to be a satisfactory screen for further Roentgen ray when large numbers of individuals can be examined in rapid succession. It is certainly superior to physical examination and has the advantage of being a record which can be reviewed or filed for further study. However, it shares with the celluloid film the disadvantage of requiring expensive apparatus, additional personnel, space, etc.—the items which determine the cost of a Roentgen ray film. In our own case the saving produced by using paper films would be too slight to offset the disadvantage that they do not produce roentgenograms of the same clearness as do celluloid films.

The basis of selection for Roentgen ray examination used at our Home Office in its medical examination of applicants for employment is fluoroscopy. After a careful history-taking (in which the patient may willfully or unconsciously conceal important facts) and after a routine physical examination, each applicant is fluoro-

scoped by the examining physician following a prescribed technique. Every suspicious or positive case is referred for Roentgen ray films. Before analyzing our results, we would like to point out some of the advantages of the fluoroscopic examination *per se*.

1. It has special diagnostic value in determining the mobility of the diaphragm and the range of expansion of the lungs. We recall a case of very early tuberculosis barely perceptible on the Roentgen ray films which was noted on the fluoroscopic examination because of the easily apparent splinting of the ribs over the lesion.

2. During the fluoroscopic examination, it is possible to observe the chest from many angles and thus to view the areas close to the heart and mediastinum which are difficult to record in the film. Occasionally a small lesion can be detected by fluoroscopy while rotating the patient, since the rays strike the lesion at the most advantageous angle. The patient can be viewed in the antero-posterior as well as in the posteroanterior diameter. By way of illustration, we have seen a cavity, 1 cm. in diameter, picked up on fluoroscopic examination in the posteroanterior position which was visible on only 1 of a pair of stereoscopic films. It is possible for a serious infiltration to be concealed by the clavicle and ribs in 1 film, but visible on the other of a stereoscopic pair. Furthermore, during a fluoroscopic examination, the chest may be viewed with scapulæ rotated out of the lung fields; the clavicles may be elevated or lowered; thick neck muscles may be pushed aside in order to view the infraclavicular regions and posterolateral 3d and 4th interspaces, where many of the rapidly progressive tuberculous infiltrations of early adult life begin. In our experience the fluoroscopic examination carefully performed will miss very few cases.

From an administrative point of view, fluoroscopy has many definite advantages: (1) The equipment is relatively inexpensive and the upkeep low. (2) The technique of fluoroscopic examination is readily acquired. Our fluoroscopic examinations are made by our examining physicians, who, after a short training period perform the examinations effectively (the majority have had no previous fluoroscopic experience). (3) The decision regarding the examination is immediate and there is no delay. We believe that the fluoroscopic examination is a cheaper method than the taking of a single flat film, is more rapid and is approximately as accurate.

We have determined our percentage of error by routinely comparing the fluoroscopic findings on a group of persons with the Roentgen ray reading. At their annual examination, chest Roentgen ray and fluoroscopic examinations have been made of 1035 employees who had not been under observation and were supposedly healthy. Among the 1035 were 47 cases which showed some abnormality, such as a cervical rib, azygos lobe, diaphragmatic pleurisy, tuberculosis, enlarged heart or aorta, foreign body, etc. We found that in 1035 examinations only 2 cases of tuberculosis of clinical

significance were missed on the fluoroscopic examination and these were very minimal cases. On the other hand, we find the fluoroscopists describing and naming abnormalities, such as the azygos lobe, accurately 6 times out of 7. We are satisfied that our percentage of error is very small.

In the campaign against tuberculosis in the German universities, fluoroscopy is considered to be a very important, if not the most important, part of the examination. In fact, since the summer semester of 1930, the fluoroscopic examination has been obligatory at the University of Munich. Doctor Kattentidt, in charge of Student Health at Munich, states: "It was experienced everywhere that the preceding clinical examination detected only a small fraction of the tuberculosis cases which were found by the fluoroscopic examination;" and further: "Dr. V. Romberg proved that 95% of all the cases detected by Roentgen ray pictures can also be diagnosed by fluoroscopic examination."[13]

In Lemberg, Poland, fluoroscopy of all newly matriculated students of all 5 colleges was introduced in 1930 and has been continued since. The method is being adopted rapidly by other universities: Münster, in Westphalia; Lund, Sweden; Heidelberg, etc.

Doctor Braeuning makes a statement with which we are in complete accord, *i. e.*, "Every department should have its own fluoroscope, and this examination should be made by the department staff and not by the central Roentgen ray department."[11]

We believe, in analyzing our experience* with fluoroscopy since 1927, that it has been a very valuable procedure. Prior to October 1, 1927, applicants for employment received a complete physical examination routinely and were Roentgen rayed only if suspicious symptoms or signs were elicited at this examination; each year several employees who had been in service less than 1 year developed active tuberculosis (in 1927, with an average clerical payroll of 9582, there were added 3094 employees; in the same year there were 11 cases of pulmonary tuberculosis among employees of less than 1 year's service, *i. e.*, 35.5 new cases per 10,000 new employees). After the fluoroscopic examination was introduced, we consistently discovered each year by this method 1% of tuberculosis among our applicants for employment (Table 1) and the number of new cases in employees of less than 1 year of service has decreased materially. (In 1932, with an average clerical payroll of 11,814 and 1707 new employees, there was only 1 case of tuberculosis among employees of less than 1 year's service, *i. e.*, 5.8 per 10,000 new employees.)

The fluoroscope has detected, therefore. those cases of tuberculosis among applicants who, in the past, had escaped detection at their preëmployment examination and who became, many of them, cases of active tuberculosis within the first year of employment.

* Approximately 17,000 fluoroscopic examinations are made each year by physicians in the Medical Department of our Home Office.

TABLE 1.—INCIDENCE OF TUBERCULOSIS AMONG APPLICANTS FOR EMPLOYMENT.

Year.	Number of applicants.	Cases of tuberculosis.*					
		Total.	Detected by			Incidence of Tbc. per 1,000.	Detected only through fluoroscopy (per cent).
			History.	Physical signs.†	Fluoroscopy.		
1928	4405	69	9	7	50	15.6	76
1929	4780	57	6	6	45	11.6	79
1930	3105	36	3	1	32	11.2	91
1931	2175	33	2	4	27	12.44	82
1932	2134	32	2	0	30	14.0	96

* In addition, the following chest conditions other than tuberculosis escaped physical examination but were detected with the fluoroscope; thymoma; substernal thyroid, 2; esophageal pouch, 1; enlarged aorta, 2; enlarged heart, 1; calcified pleura, 1; adhesive pleurisy, 4.

† The physical examination is checked, if there are abnormal fluoroscopic findings. However, the number of corrections is surprisingly low, even though the examiner knows the area in which the lesion is located.

The incidence of new cases of tuberculosis among our employees has also been reduced (Table 2):

TABLE 2.—INCIDENCE OF NEW CASES OF TUBERCULOSIS* AMONG H. O. EMPLOYEES.

Year.	H. O. Employees.	New cases of Tbc.	Cases per 10,000.
1928	11,530	106	92
1929	11,966	85	71
1930	12,468	71	71
1931	13,081	72	57
1932	13,582	59	43

* Including active, questionably active and apparently healed.

An even greater result has been accomplished in respect to the early diagnosis of tuberculosis. Using the fluoroscope freely at annual examinations and in the medical rest rooms, we have been able to detect tuberculosis in its early stages, so that the cases admitted to our Sanatorium in 1932 were 76% incipient and 24% advanced, while in 1928, 47% were incipient and 53% advanced.

Fluoroscopy has been subjected to criticism as to its accuracy because of the fact that active tuberculosis has developed among young adults who apparently had a negative fluoroscopic examination a short time previously, the conclusion being that the fluoroscope failed to reveal definite disease which must have been present. This is not necessarily true. We have seen many who have developed definite Roentgen ray evidence of tuberculosis after a negative film of the chest, some within 3 months of the negative film.

Dr. Braeuning reports 19 cases of tuberculosis under his observation which had developed between $2\frac{1}{2}$ to 12 months after a negative Roentgen ray;[11] Dr. Rist, of the Laennec Hospital in Paris, states he

has had apparently normal Roentgen rays of lungs a few days previous to the onset of extended tuberculosis.[14]

Summary. The most reliable method of detecting pulmonary tuberculosis is by means of the Roentgen ray film, but as a routine procedure in examining large numbers of supposedly healthy individuals, it has the disadvantage of being expensive. We have discussed the various methods available for selecting those cases which shall have films made.

Physical examination of the chest fails to detect many, especially early, cases of pulmonary tuberculosis.

A case-finding method based upon history is also inadequate, since tuberculosis may be present to an advanced degree without significant symptoms.

The tuberculin test is of considerable value in selecting those cases of childhood tuberculosis which shall have Roentgen ray films, but its application to adults is less satisfactory because of the large percentage of reactors.

Paper films at their present stage of development do not produce roentgenograms of the same clearness as celluloid; the cost of the finished product is only slightly less than that of the celluloid.

Fluoroscopy as a method of examination has many advantages which have been described. Moreover, it is inexpensive and the technique easily acquired. Its accuracy has been demonstrated by determining our percentage of error in 1035 cases first fluoroscoped, then filmed, and finding it very low. Its practical value to us has been proved by an analysis of our tuberculosis statistics during the 5 years this method has been used. These statistics show that: (1) We have detected each year among applicants for employment 1% of tuberculosis which would otherwise have escaped discovery; (2) we have reduced our incidence of new cases of tuberculosis from 92 per 10,000 in 1928 to 43 per 10,000 in 1932; (3) we are detecting tuberculosis in the early stages; sanatorium admissions in 1928 were 47% minimal; in 1932, 76% minimal.

Conclusion. The Roentgen ray film examination of the chest is the most reliable method available for detecting pulmonary tuberculosis. Fluoroscopy, by reason of its accuracy, economy, rapidity and simplicity of technique, is the most efficient basis of selection for complete roentgenographic examination.

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THE RELATIONSHIP OF THE INTRINSIC FACTOR TO A HEMATOPOIETIC MATERIAL IN CONCENTRATED HUMAN GASTRIC JUICE.

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It has been shown[1] that the incubation of 100 cc. of normal gastric juice with 1 vial of Liver Extract No. 343 markedly increases the potency of the liver extract. This increase in potency is probably the result of the interaction of the intrinsic factor of the gastric juice upon an extrinsic factor in the liver extract. Because of the uniformity of the product and its small bulk, the liver extract would seem to be a better source of the extrinsic factor than beef muscle in testing for the presence of the intrinsic factor. In previous studies[2] it has been shown that before a hematopoietically stimulating material can be demonstrated in normal human gastric juice by the intramuscular injection into patients having pernicious anemia, some change in the gastric juice must take place. This change can take place during the concentration by vacuum distillation or during the storage of the gastric juice in the ice box for 2 months.

It is the purpose of this paper to report studies on the relationship of the intrinsic factor to the hematopoietic material in concentrated human gastric juice and attempts to determine some of the characteristics of the intrinsic factor.

Methods. The patients used in these studies were all typical clinically and hematologically of pernicious anemia. Daily red blood cell counts, hemoglobin determinations (Newcomer) and reticulocyte counts were made during the control and test periods. One vial of Liver Extract No. 343 was incubated for 4 hr. at 40° C. with the gastric juice, or the fraction of gastric juice, to be tested, as described previously.[1] These liver extract gastric juice digests were brought to pH 5 just previous to administration to the patients. During the test periods the patients received meat-free,

low vitamin B_2 diets. The patients received the noon meal at 11 A.M. and then received no food until 6.30 P.M. At 4.30 P.M. the gastric juice liver extract digests were administered. All the patients received the test materials daily for 10 days. The patients who had slight or no responses from the test materials responded to known potent materials administered by mouth before the experiments were considered negative.

The ultrafilters used were of the Bechold type described previously.[2] When the gastric juice was concentrated by vacuum distillation, the same procedure as in the preceding paper[2] was carried out. When the pepsin and rennin were adsorbed on casein, a method similar to that described by Hammarsten[3] was used. A 7.5% solution of Hammarsten casein in 4% sodium carbonate was added to a known quantity of gastric juice until a pH of 4.7 to 5 was obtained, which is the point of maximum precipitation. The casein precipitate was removed by centrifugalization and filtration. The filtrate is water-clear and filters rapidly. By the methods employed, no pepsin and only insignificant amounts of rennin could be detected in the filtrate. When the casein precipitate was used in the experiments, it was washed by stirring the precipitate with a buffer at pH 4.7, centrifuging and decanting the wash fluid.

Results. I. *The Effect of the Incubation of Varying Amounts of Normal Human Gastric Juice upon the Potency of Liver Extract.* In Table 1 are recorded the responses of the red blood cells, hemoglobin, and reticulocytes to the daily administration of 1 vial of liver extract that had been incubated with 10, 25 and 50 cc. of normal human gastric juice and to the subsequent administration of Extralin. The responses of the reticulocytes of Case 1 to the liver extract incubated with 10 and 25 cc. were distinctly not maximal (9.6% and 8.1% at red blood cell levels of 1.55 and 2.02 million). There was only slight clinical improvement and no sustained rise in red blood cells. There was a good clinical and hematologic response after the patient received Extralin, capsules 4 t. i. d., a. c. There was a good clinical improvement when Case 2 received daily 1 vial of liver extract which had been incubated with 50 cc. of gastric juice. The reticulocytes reached 17.2% on the 9th day when the red blood cell count was 2 million, and there was only a slight rise (3.4%) following the subsequent administration of Extralin.

These studies would indicate that 10 and 25 cc. of normal human gastric juice did not contain sufficient intrinsic factor to react with 1 vial of liver extract to produce a maximal reticulocytosis. However, it is interesting that as little as 10 cc. increases the potency of liver extract enough to cause a slight reticulocytosis. Fifty cc. seems to be near the minimal amount of gastric juice necessary to combine with 1 vial of liver extract. These findings indicate that there must be some quantitative relationship between the amounts of intrinsic and extrinsic factors present to produce maximal reticulocyte responses. Castle and his associates[4] demonstrated that 75 cc. of the juice is sufficient to interact with 200 gm. of beef muscle. Therefore, somewhere between 50 and 75 cc. should be the minimal amount necessary to combine with 1 vial of liver extract to produce a maximal reticulocytosis.

TABLE 1.—THE RESPONSE OF THE BLOOD TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT NO. 343 INCUBATED WITH 10, 25, AND 50 CC. OF NORMAL HUMAN GASTRIC JUICE.

Case number		1			1			2	
Age		62			62			39	
No. cc. G. J. incubated with 1 vial of L. E. No. 343		10			25			50	
	Days.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.
	0	1.65	31	0.1	1.46	30	5.2	1.44	34	1.0
	1	1.73	31	0.6	1.55	35	4.5	....	..	0.8
	2	1.43	35	0.6	....	..	6.1	1.72	32	0.6
	3	1.58	31	0.6	2.02	34	8.1	1.67	32	0.4
	4	1.34	26	1.0	1.61	39	3.5	1.53	32	0.8
	5	....	..	....	1.53	39	2.3	1.79	37	2.8
	6	1.25	27	2.6	1.46	40	4.4	....	..	6.9
	7	1.44	30	4.8	1.52	42	5.1	1.50	30	14.6
	8	1.55	31	9.6	1.56	42	2.6	1.94	33	17.4
	9	1.48	31	5.3	....	..	5.7	2.00	32	17.2
	10	1.46	30	5.2	1.70	42	8.4	1.93	38	15.6
	11	....	..	....	....	..	....	2.15	41	14.1
	12	....	..	....	....	..	....	2.31	38	10.1
	13	....	..	....	....	..	....	....	..	13.8
	14	....	..	....	....	..	....	2.51	42	12.8
	15	....	..	....	....	..	....	2.40	44	11.6
	16	....	..	....	....	..	....	2.37	47	7.7
	17	....	..	....	....	..	....	2.38	47	5.0
	18	....	..	....	....	..	....	2.84	50	4.3
Subsequent medication					Extralin, caps. 4 t. i. d.			Extralin, caps. 4 t. i. d.		
	0	....	..	....	1.70	42	8.4	2.84	50	4.3
	1	....	..	....	1.81	42	8.0	2.54	44	2.5
	2	....	..	....	2.02	44	6.3	....	..	3.7
	3	....	..	....	1.94	47	6.9	2.63	47	1.8
	4	....	..	....	2.18	50	12.7	2.44	50	1.5
	5	....	..	....	2.17	49	11.9	2.48	55	1.8
	6	....	..	....	....	..	13.7	2.91	55	3.0
	7	....	..	....	1.83	53	7.7	2.98	50	3.4
	8	....	..	....	1.98	52	5.5			
	9	....	..	....	2.25	58	7.6			

* Newcomer method.

II. *The Effect of Gastric Juice Concentrated by Ultrafiltration and the Ultrafiltrate of Normal Gastric Juice upon the Potency of 1 Vial of Liver Extract.* Case 3 first received for 10 days 1 vial of liver extract that had been incubated with 150 cc. of the portion of the normal human gastric juice which passed through the ultrafilters (ultrafiltrate). The concentration of pepsin in the original gastric juice averaged 4.2 mg. and rennin 42 mg. per cc. The ultrafiltrate contained 0.1 mg. of pepsin and 1 mg. of rennin per cc. Chart I shows that there was a slight reticulocyte rise (3.4%) following this medication; however, there was no clinical improvement. The patient then responded to 1 vial of liver extract that had been incubated with the portion of this gastric juice which was held back by the ultrafilters (concentrate). The reticulocytes reached 10.1% on the 7th day, when the red blood cell count was 3.01 million. There was satisfactory clinical improvement and a good rise in red blood cells and hemoglobin, as is shown in Chart I.

These studies showed that almost all of the intrinsic factor had been held back by the ultrafilters. In the previous work it was shown that the portion of the gastric juice held back by the ultrafilters could be made hematopoietically active, as demonstrated by the intramuscular injection into patients having pernicious anemia, when concentrated by vacuum distillation, while the ultrafiltrate could not be made active by the same procedure. Therefore, from the above tests it can be assumed that the portion of the gastric juice which can be made active for intramuscular injection contains the intrinsic factor at the onset of the vacuum distillation and the portion which cannot be made active does not.

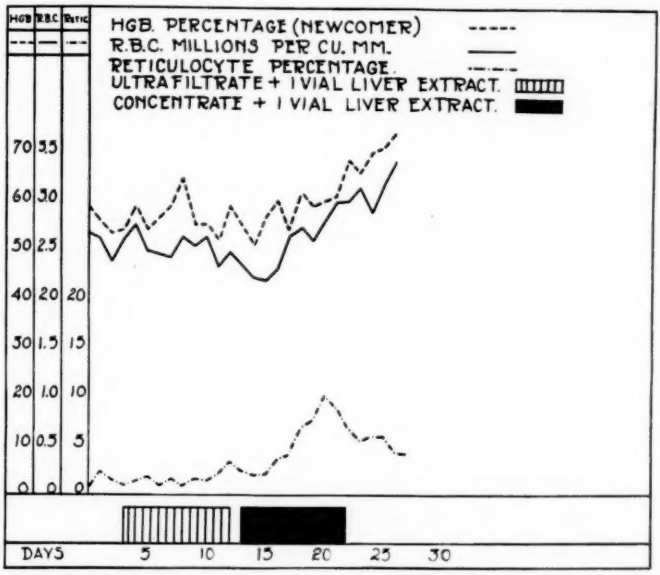

CHART I.—Response (Case 3) to the daily administration of 1 vial of Liver Extract No. 343 incubated with the ultrafiltrate of normal human gastric juice and to 1 vial of Liver Extract No. 343 incubated with the portion of the gastric juice concentrated by the ultrafilters.

III. *The Effect of the Incubation of Gastric Juice Concentrated by Vacuum Distillation and then Diluted with Water upon the Potency of Liver Extract.* Fresh human gastric juice (1200 cc., divided into 2 equal parts) was concentrated to 21 cc. by vacuum distillation and then diluted to 1000 cc. The concentration of pepsin in the original gastric juice averaged 4.4 mg. and rennin 49 mg. per cc. The gastric juice after concentration by vacuum distillation and dilution with water contained 1.3 mg. of pepsin and 9 mg. of rennin per cc. Of this material 100 cc. was incubated with 1 vial of liver extract and administered daily to Case 4. There was a slight reticulocytosis (8% on the 11th day when the red blood cell count was 2.21 million and the hemoglobin 48%), but there was little or no

clinical improvement. Table 2 shows the responses of the blood to this medication and to Extralin. This patient had a rather high reticulocyte count on entering the hospital; however, after a 7 days' control period the red blood cell count had dropped from 2.27 to 1.85 million, although the reticulocyte count was still 3%. A very good clinical response and reticulocytosis of 27% (red blood cell count 2.21 million) followed the administration of Extralin. There was also a good rise in red blood cells.

TABLE 2.—THE RESPONSES OF THE BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT NO. 343 INCUBATED WITH NORMAL HUMAN GASTRIC JUICE CONCENTRATED BY VACUUM DISTILLATION AND THEN DILUTED.

Case number		4			5			5		
Age		46			66			66		
Enzymes in original G. J. (aver. mg. per cc.)		Pepsin 4.4 Rennin 49.0			Pepsin 2.9 Rennin 32.0			Pepsin 2.9 Rennin 32.0		
Enzymes in G. J. after vacuum distillation (aver. mg. per cc.)		Pepsin 1.3 Rennin 9.0			Pepsin 1.95 Rennin 22.0			Pepsin 1.95 Rennin 22.0		
Enzymes in ultrafiltrate (aver. mg. per cc.)		.....			Rennin 0.8					
Material derived from No. cc. G. J. incubated with 1 vial of L. E. No. 343		120			120			120		
	Days.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.
	0	1.85	38	3.0	2.01	49	1.4	....	53	0.6
	1	2.13	38	3.0	....	..	1.0	1.90	49	1.3
	2	2.17	43	2.7	2.00	53	0.7	1.83	49	1.7
	3	1.79	44	2.5	1.99	53	0.8	2.07	45	2.2
	4	1.76	45	2.4	2.11	53	0.4	1.95	47	1.7
	5	2.04	42	4.0	2.07	51	0.5	....	..	2.4
	6	....	..	2.7	2.02	49	0.3	1.80	45	3.6
	7	2.04	39	4.4	1.90	53	0.8	1.95	..	2.2
	8	1.90	45	5.7	1.51	..	0.8	1.72	..	1.2
	9	2.11	41	5.8	2.11	53	1.2	1.70	47	2.9
	10	2.10	40	6.4	....	53	0.6	2.01	43	2.1
	11	2.21	47	8.0	....	..	...	1.83	42	2.0
	12	1.90	50	5.8	....	..	...	....	..	2.5
	13	....	..	3.5	....	..	...	2.21	43	1.8
	14	2.03	44	3.4						
	15	1.97	45	2.0						
	16	1.61	40	1.0						
Subsequent treatment		Extralin, caps. 4 t. i. d.						Extralin, caps. 4 t. i. d.		
	0	1.61	40	1.0	....	..	...	2.21	43	1.8
	1	2.15	42	2.8	....	..	...	1.80	44	1.6
	2	1.59	44	4.0	....	..	...	1.66	43	2.8
	3	1.79	38	4.9	....	..	...	1.93	42	2.0
	4	....	..	9.8	....	..	...	1.83	43	11.2
	5	1.85	40	25.6	....	..	...	1.86	43	12.8
	6	2.21	..	27.0	....	..	...	....	..	14.8
	7	2.17	47	22.4	....	..	...	....	..	23.8
	8	2.83	41	23.6	....	..	...	1.93	43	21.8
	9	3.25	54	12.6	....	..	...	2.50	47	15.2
	10	2.65	54	17.0	....	..	...	2.94	55	13.2
	11	....	..	12.4	....	..	...	2.36	54	8.8
	12	3.18	53	11.7	....	..	...	2.72	59	9.0
	13	2.88	50	13.3	....	..	...	2.61	59	9.6
	14	....	..	....	....	..	...	2.96	61	4.9
	15	....	..	....	....	..	...	3.09	62	

* Newcomer method.

Another 1200 cc. of fresh gastric juice (divided into 2 equal parts) was concentrated to 30 cc. by vacuum distillation and then diluted

to 1000 cc. The original gastric juice contained 2.9 mg. of pepsin and 32 mg. of rennin per cc. The gastric juice after concentration by vacuum distillation and dilution contained 1.95 mg. of pepsin and 22 mg. of rennin per cc. The gastric juice was then ultrafiltered. Of the ultrafiltrate 100 cc. was incubated with 1 vial of liver extract and administered daily to Case 5. As is shown in Table 2, there was no response of the blood or improvement in the clinical condition of the patient. The portion of the gastric juice held back by the ultrafilters was then diluted to 1000 cc. and 100 cc. of this was incubated with 1 vial of liver extract and administered daily to Case 5. This medication was followed by a rise in the reticulocytes up to 3.6% by the 6th day; but at the end of 13 days there was only slight change in the red blood cell level and no improvement in the condition of the patient. There was then a rise in reticulocytes up to 23.8% on the 7th day of Extralin therapy. There was a very satisfactory clinical improvement and rise in red blood cells and hemoglobin (Table 2).

It is evident from these findings that most of the intrinsic factor is either destroyed or used up during the process of concentration by vacuum distillation. The concentration by vacuum distillation, however, is necessary for the production of the material in the human gastric juice capable of stimulating the hematopoietic system of patients having pernicious anemia when injected intramuscularly. A goodly percentage of the pepsin and rennin in the gastric juice was likewise destroyed by the process of concentration by vacuum distillation.

The small amount of intrinsic factor remaining in the gastric juice concentrated by vacuum distillation was held back by the ultrafilters, while most of the material in the concentrated gastric juice which is active when injected passed through the filters.[2] It would therefore seem more evident that these two materials are not the same, although it has not been shown as yet that the intrinsic factor does not combine with some extrinsic factor during the concentration by vacuum distillation to form the material hematopoietically active when injected.

IV. *Studies on the Intrinsic Factor Freed from Pepsin and Rennin by Casein Precipitation.* In this group of studies the enzymes pepsin and rennin of the gastric juice were precipitated out on casein at pH 4.7 as described under "Methods."

Case 6 received daily for 10 days 1 vial of liver extract which had been incubated with the precipitate containing 3.7 mg. of pepsin and 33 mg. of rennin per cc. after the precipitate had been redissolved in 0.3% hydrochloric acid and brought up to the original volume of the gastric juice. Of this material 125 cc. was used daily. There was a rise in reticulocytes up to 5.6% (red count 1.77 million) on the 6th day, but there was no rise in red blood cells or improvement in the condition of the patient.

The amount of supernatant liquid (containing 0 mg. pepsin and

0.05 mg. rennin per cc.) equivalent to 125 cc. of the original gastric juice was incubated with 1 vial of liver extract and administered daily for 10 days to Case 7. Table 3 shows the marked reticulocyte rise (37.4% at a red blood cell level of 1.76 million) following this therapy. There was a very satisfactory improvement in the clinical condition and a rise in red blood cells. There was no subsequent rise in reticulocytes following 3 daily intramuscular injections of concentrated liver extract.

These tests showed conclusively that most of the intrinsic factor remained in the supernatant liquid, although the pepsin and rennin was completely precipitated out of the liquid. Castle and his associates[5] in similar experiments, using beef muscle as the source of the extrinsic factor, reported that the intrinsic factor could be separated from the enzymes pepsin and rennin by casein precipitation.

Case 8 received 150 cc. of this supernatant liquid daily for 10 days to see if by the casein precipitation a material itself hematopoietically active was released, rather than that there was just a separation of the intrinsic factor from the other constituents of the gastric juice. There was no reticulocytosis following this medication and no change in the clinical condition. After 2 other test periods this patient responded to Extralin, capsules 4 t. i. d., a. c. (reticulocytes 11% at a red blood cell level of 2.86 million) as is shown in Table 3.

Supernatant fluid from another casein precipitation of the gastric juice was then subjected to ultrafiltration. The ultrafiltrate (equivalent to 120 cc. of original juice) was incubated with 1 vial of liver extract and administered daily to Case 6. On the 7th day of this treatment the reticulocytes reached 14.1% (red blood cell count 2.03 million). There was a good rise in red blood cells, as is shown in Table 3, and definite clinical improvement. After 16 days the patient received for 3 days 3 cc. of concentrated liver extract intramuscularly. This was followed by a reticulocytosis up to 4.6% and a further rise in red blood cells.

The portion of this supernatant fluid that was held back by the ultrafilters was then diluted with water. In amounts equivalent to 120 cc. of the original gastric juice it was incubated with 1 vial of liver extract and administered daily for 10 days to Case 9. There was a rise in reticulocytes up to 6.6% by the 8th day (red blood cell count 2.58 million). There was definite clinical improvement and the red blood cell count made a very satisfactory increase (see Table 3). There was no subsequent rise in reticulocytes following the administration of Extralin.

In the studies in Section II it was shown that practically all the intrinsic factor in normal gastric juice had been held back by the ultrafilters. However, the experiments in Section IV demonstrate that after the precipitation of the pepsin and rennin and mucus by casein, a goodly portion of the intrinsic factor passes through the filters. This indicates that by the casein precipitation the intrinsic

TABLE 3.—THE RESPONSES OF THE BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT NO. 343 INCUBATED WITH NORMAL HUMAN GASTRIC JUICE AFTER CASEIN PRECIPITATION OF THE GASTRIC JUICE.

TABLE 3.—THE RESPONSES OF THE BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO THE DAILY ADMINISTRATION OF ONE VIAL OF LIVER EXTRACT NO. 343 INCUBATED WITH NORMAL HUMAN GASTRIC JUICE AFTER CASEIN PRECIPITATION OF THE GASTRIC JUICE.

		6			7			8†			6			9		
Case number																
Age		58			63			56			58			45		
Enzymes in original G. J. (aver. mg. per cc.)		Pepsin 5.2 Rennin 54.0			Pepsin 5.2 Rennin 54.0			Pepsin 2.9 Rennin 32			Pepsin 4.9 Rennin 62			Pepsin 4.9 Rennin 62		
Enzymes in precipitate (aver. mg. per cc.)		Pepsin 3.7 Rennin 33.0			Pepsin 3.7 Rennin 33.0											
Enzymes in supernatant fluid (aver. mg. per cc.)		Pepsin 0 Rennin 0.05			Pepsin 0 Rennin 0.05			Pepsin 0 Rennin 0.1			Pepsin 0 Rennin 0.14			Pepsin 0 Rennin 0.14		
Fraction of G. J. used		Precipitate			Supernatant fluid			Supernatant fluid			Ultrafiltrate of supernatant fluid			Concentrate of supernatant fluid		
Material derived from No. cc. G. J. incubated with 1 vial of L. E. No. 343		125			125			150 (no L. E.)			120			120		
	Days.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.	R. B. C. per cmm. in millions.	Hgb. %.*	Ret. %.
	0	2.04	44	0.5	97	24	3.7	2.19	49	0.1	....	..	3.5	2.24	44	1.1
	1	2.05	40	0.5	99	23	4.0	2.28	46	0.1	1.96	45	3.4	2.37	49	
	2	2.13	51	1.3	....	..	3.9	2.20	43	0.4	1.98	45	2.4	....	..	1.5
	3	....	..	1.2	1.08	24	5.3	2.03	44	0.4	2.00	47	3.0	2.28	50	0.5
	4	1.93	44	1.5	98	23	10.2	....	..	0.2	2.15	45	6.5	2.67	54	1.0
	5	....	..	1.8	95	21	9.5	1.94	50	0.4	2.23	43	7.4	2.11	45	2.3
	6	1.77	47	5.6	1.06	28	22.0	1.90	46	0.0	2.01	49	10.4	2.13	53	3.8
	7	1.94	47	3.4	1.03	26	29.8	1.71	46	0.4	2.03	..	14.1	2.63	57	4.5
	8	1.84	49	3.4	1.35	..	38.3	1.77	43	0.2	2.48	53	10.8	2.58	53	6.6
	9	1.93	40	3.7	1.76	..	37.4	1.79	46	0.2	2.59	62	7.9	....	..	6.4
	10	....	..	3.5	1.91	27	20.0	1.65	41	0.2	2.75	55	10.0	2.60	50	5.0
	11	....	..	....	....	..	20.0	....	..	....	2.88	59	7.1	2.80	55	5.1
	12	....	..	....	1.64	35	11.0	....	..	....	3.10	50	....	2.53	55	5.5
	13	....	..	....	2.07	37	10.0	....	..	....	2.68	57	6.1	2.93	55	4.4
	14	....	..	....	2.24	37	3.1	....	..	....	....	..	4.3	2.95	55	2.3
	15	....	..	....	2.35	36	5.0	....	..	....	2.83	61	3.6	3.11	59	
	16	....	..	....	....	..	2.6	....	..	....	2.88	65	2.5			
	17	....	..	....	2.25	41	1.0									
Subsequent treatment					Conc. L. E., 3 cc. (3 daily doses)			Extralin, caps. 4 t. i. d.			Conc. L. E., 3 cc. (3 daily doses)			Extralin, caps. 4 t. i. d.		
	0	....	..	....	2.25	41	1.0	....	..	5.2	2.88	65	2.5	3.11	59	
	1	....	..	....	2.59	47	1.7	2.63	55	4.8	2.94	74	2.4	....	..	3.8
	2	....	..	....	3.11	43	..	2.33	50	3.2	3.01	60	1.3	3.01	53	1.4
	3	....	..	....	2.39	45	0.7	2.12	40	2.4	3.11	63	2.8	2.92	64	1.4
	4	....	..	....	2.77	47	0.7	2.24	55	5.7	3.05	71	....	2.71	65	0.4
	5	....	..	....	2.85	47	0.1	2.10	55	9.4	....	..	2.2	2.44	71	0.8
	6	....	..	....	2.62	47	1.2	2.45	57	11.0	3.19	67	3.1	2.43	60	0.8
	7	....	..	....	2.88	47	0.3	....	..	11.0	2.91	68	4.6			
	8	....	..	....	3.14	53	1.1	2.86	66	7.2	2.78	71	2.5			
	9	....	..	....	....	..	....	2.73	55	7.1	3.16	74	3.5			
	10	....	..	....	....	..	....	3.54	66	5.8	3.07	67				
	11	....	..	....	....	..	....	3.34	61	2.3	3.35	78	1.3			
	12	....	..	....	....	..	....	3.29	68	2.6						

* Newcomer method.

† This patient received 2 other test materials before responding to extralin.

factor was released or separated from some larger molecular material in the gastric juice, thus allowing it to pass through the filters.

Following these studies 400 cc. of normal gastric juice was precipitated at pH 4.7 with casein. The supernatant fluid, containing 0.08 mg. rennin per cc., was made up to pH 2 with HCl and passed through the ultrafilters and washed 3 times. This ultrafiltrate was then concentrated to 15 cc. by vacuum distillation. It was neutralized with NaOH and sterilized with tricresol and injected into Case 10 on June 22, 1933. At the beginning of the test the red blood cell count was 1.88 million, hemoglobin 35%, and reticulocytes 0.6%. There was a severe chill followed by a rise in temperature up to 104° F. The temperature remained elevated for 2 days. The reticulocytes reached 4.2% by June 26 and remained slightly above normal limits until July 2. By July 8 the red blood cell count was 1.71 million, hemoglobin 45.8%, and reticulocytes 0.9%. The patient then received 20 cc. of liver extract intravenously. This was followed by a reticulocytosis up to 20.6% by July 14. There was marked clinical improvement and by July 22, 1933, the red blood cell count was 3.15 million and the hemoglobin 51%.

The material concentrated by vacuum distillation in this test had been shown to contain a goodly amount of intrinsic factor (Case 6), and the process of concentration by vacuum distillation had previously always produced a hematopoietically active material when the intrinsic factor was present. It would therefore seem that by the casein precipitation and the ultrafiltration most of the material with which the intrinsic factor can react had been eliminated from the gastric juice.

Summary and Conclusions. From these studies it is quite evident that there must be some quantitative relationship between the amounts of intrinsic and extrinsic factors present to produce maximal reticulocyte responses when liver extract-gastric juice digests are fed to patients having pernicious anemia. The amount of intrinsic factor in from 50 to 75 cc. of normal gastric juice seems to be the minimal amount necessary to produce a maximal response when incubated with 1 vial of liver extract. The fact that as little as 10 cc. of normal gastric juice will increase the potency of 1 vial of liver extract enough to produce a slight reticulocytosis must, however, be considered when a quantitative estimation of the amount of intrinsic factor in an abnormal gastric juice is attempted, as by Hartfall, and Witts,[6] Spies and Payne,[7] and Beebe and Wintrobe.[8] The use of liver extract as the source of the extrinsic factor in such tests now seems more advisable than the use of beef muscle, because if sufficient intrinsic factor is present in the gastric juice maximal reticulocytoses can be expected when 1 vial of liver extract is used, while this is not always the case when beef muscle is used.

The intrinsic factor in normal human gastric juice does not pass through the ultrafilters used in these experiments. The material in normal human gastric juice which can be made hematopoietically

active by concentration by vacuum distillation is likewise held back. It has therefore been shown that the intrinsic factor has been present at the onset of the concentration by vacuum distillation in all the gastric juice preparations that we have made active. The material in gastric juice concentrated by vacuum distillation which is active when injected, however, is not identical with the intrinsic factor, because the intrinsic factor is destroyed or used up by the process of concentration by vacuum distillation during which the active material in concentrated gastric juice is formed. However, the ultrafiltrate of gastric juice freed from pepsin, rennin, and mucus by casein precipitation but containing the intrinsic factor, was not hematopoietically active after concentration by vacuum distillation. This would tend to support the hypothesis that the hematopoietically stimulating material in concentrated normal human gastric juice is not formed unless both an intrinsic and an extrinsic factor are present in the gastric juice during the process of concentration by vacuum distillation.

These experiments confirm the work of Castle and his associates in that the intrinsic factor can be separated from the enzymes pepsin and rennin by casein precipitation. They also tend to show that the intrinsic factor is of relatively small molecular structure after it is freed from the pepsin, rennin, and mucus by the casein precipitation.

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THE RÔLE OF THE LIVER IN HEMATOPOIESIS.

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During recent years a series of observations on the treatment of pernicious anemia has helped to clarify many points concerning the normal physiology of the liver and its relation to blood forma-

tion. Beginning with the work of Minot and Murphy,[1] in 1926, on the beneficial effect of liver substance in the treatment of pernicious anemia, subsequent workers[2] have demonstrated that a similar response could be obtained by the feeding of desiccated defatted hog stomach. The hypothesis was that after eating ground, dried stomach, a material was produced which was converted into a material similar to that derived from liver, and the excess was stored in the hepatic tissues. Richter, Ivy and Kim[3] concluded that the "active substance" was not an integral part of liver tissue, but a storage product which could be released when needed, to govern hematopoiesis. Confirmatory evidence of the function of the liver as a storehouse rather than as a source of a specific protein or some other substance contained in its own cellular makeup was obtained by the finding of livers which did not contain the "active material." The clue to this was given by the fact that some patients with cirrhosis of the liver had an anemia with red blood cells larger than normal. Others, with evident hemorrhage, simulated the "secondary" types of anemia.

The following experiments were developed to (1) explain why some patients with disease of the liver developed an anemia with large red blood cells, and (2) to note the curative effect of adequate therapy with liver extract on this type of anemia.

Materials and Methods. The patients studied in these experiments were classical cases of pernicious anemia, as evidenced by finding in all of an achylia gastrica, characteristic blood pictures, and definite clinical features as glossitis and neurologic changes. The blood counts were made with pipettes certified by the U. S. Bureau of Standards. Hemoglobin estimations were made with Leitz hemoglobin standard, calculated so that 14 gm. = 100%. This was checked in accordance with van Slyke's gas method. The immature red cells (reticulocytes) were studied from films stained with the vital dye, brilliant cresyl blue. All the extracts were prepared from human livers, according to the chemical method previously described.[4] Control periods of at least 2 days were obtained in each instance to rule out the possibility of spontaneous remissions.

The Active Principle Present in Liver Tissue at the Time of Birth or Shortly Before. Experiment I. A chemically refined extract was prepared from a 7-month human fetal liver. The final dosage of 20 cc., representing 65 gm. of fresh liver, was administered to a patient with typical pernicious anemia, whose blood picture on admission was as follows: Red blood cell count, 950,000 per cmm.; white blood cell count, 3600 per cmm.; hemoglobin, 25% (Sahli). On the 7th day following treatment a reticulocyte peak of 17.6% was noted. Although the maximum calculated reticulocyte response[5] was not obtained, the results are certainly indicative that at 7 months a human fetal liver contains the active principle necessary for red cell development. (Chart 1.)

The Active Principle Absent From the Liver of an Inadequately Treated Case of Pernicious Anemia. Experiment II. A parenteral extract was prepared, similar to the above described, from the human liver of a patient with pernicious anemia, who had shown only slight improvement with antianemic therapy, and died subsequently with severe complications. On admission his red cell count was 2,100,000 per cmm.; hemoglobin, 58% (Sahli, 14 gm. = 100%); the film showed marked poikilocytosis and anisocytosis with 58.5% of the red cells larger than 7.5 microns.

This intravenous product was given to a patient with pernicious anemia, whose red cell count was 1,560,000 per cmm.; white blood cell count, 6900 per cmm.; hemoglobin, 29% (Sahli). No response was noted after an interval of 12 days. When a known potent parenteral extract was administered later to this same patient, a maximum reticulocyte response of 52.8% was obtained. The absence of any response following the initial treatment was probably the result of the failure of the body of the patient from whom the liver was taken to produce or store the necessary hematopoietic factor. A similar experiment was performed by Richter *et al.*,[3] who also demonstrated that a liver from an inadequately treated case of pernicious anemia did not contain the active principle. (Chart 2.)

The Active Principle Present in the Liver of an Adequately Treated Case of Pernicious Anemia. Experiment III. A third extract was prepared from the liver of a patient with pernicious anemia who received a maximum amount of treatment for a period of 18 days, but died following an operation. At the time of admission the red cell count was 2,900,000 per cmm.; hemoglobin, 53% (Sahli). Five days after therapy was started the reticulocytes reached a maximum response of 12.5%. When this preparation was administered intravenously to a patient having pernicious anemia (red blood cell count, 1,630,000 per cmm.; white blood cell count, 4500 per cmm.; hemoglobin, 41%), a prompt subjective improvement resulted as well as a maximum reticulocyte response of 21.9%. This experiment, demonstrating the presence of the active principle in the liver of a patient with pernicious anemia, who had adequate therapy, fully substantiates the work of Richter, Ivy and Kim. (Chart 3.)

A Cirrhotic Liver May Not Contain the Active Principle. Experiment IV. A human liver was obtained from a patient dying of atrophic cirrhosis of the liver. His blood on preliminary examination showed a red count of 1,050,000 cells per cmm.; white blood cells, 3500 per cmm.; hemoglobin, 28% (Sahli). Red cell measurements revealed a Price-Jones curve simulating that seen in pernicious anemia. A chemically purified extract was prepared in the usual manner, and given to a pernicious anemia patient with no subsequent clinical improvement or blood changes. At the time of admission her blood picture was as follows: Red blood cell count, 2,400,000 per cmm.; white blood cell count, 9200 per cmm.; hemoglobin, 62% (Sahli). After a lapse of 7 days, the same individual was treated with a known potent intravenous liver extract. Ninty-six hours after therapy was instituted, the reticulocytes reached a maximum peak of 10.8% and was accompanied by the usual symptomatic improvement. (Chart 4.)

The absence of the hematopoietic substance necessary for the maturation of the red cells is certainly suggestive that a cirrhotic liver is unable to store this material since the patient with cirrhosis also showed evidence of a lack of "active material." As will be shown later, a damaged liver may have the normal function for storage of the active principle, but for some unknown reason is unable to present it to the tissues for utilization.

Patients With Cirrhosis of the Liver and Macrocytic Anemia Respond to Parenteral Liver Extract Therapy. Experiment V. Two patients with cirrhosis of the liver (diagnosed at operation), having blood pictures simulating pernicious anemia—Case 1: red blood cell count, 1,740,000 per cmm.; white blood cell count, 3800 per cmm.; hemoglobin, 44% (Sahli); and Case 2: red blood cell count, 2,220,000 per cmm.; white blood cell count, 11,100 per cmm.; hemoglobin, 41% (Sahli)—were treated postoperatively with known potent parenteral liver extracts.[6-9] In each instance, a maximum reticulocyte response was obtained, being 36.4% and 11% respectively. One of these patients has received parenteral therapy for a period of 2 years with no recurrence of the anemia or any of

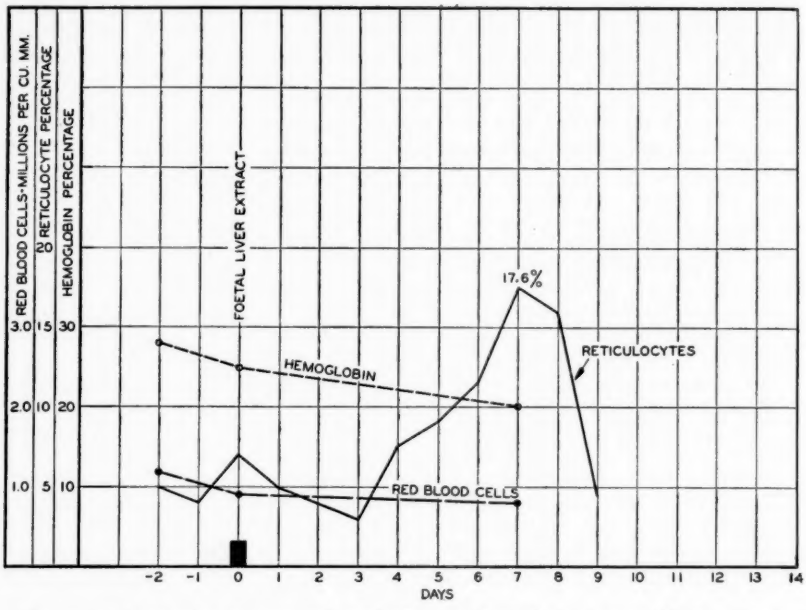

CHART 1.—Reticulocyte response with human fetal liver extract (65.0 grams.)

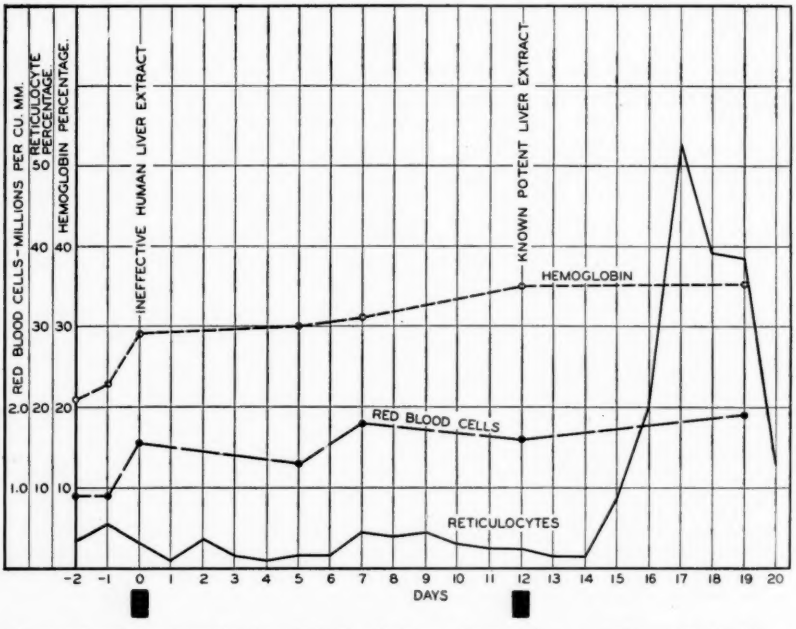

CHART 2.—Liver from inadaquately treated case of pernicious anemia—not effective.

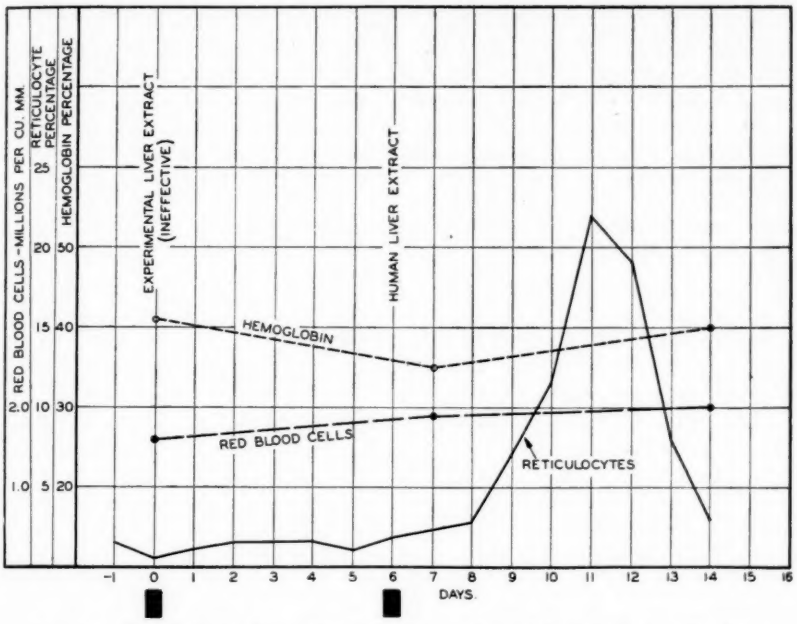

CHART 3.—Liver from adaquately treated case of pernicious anemia—effective.

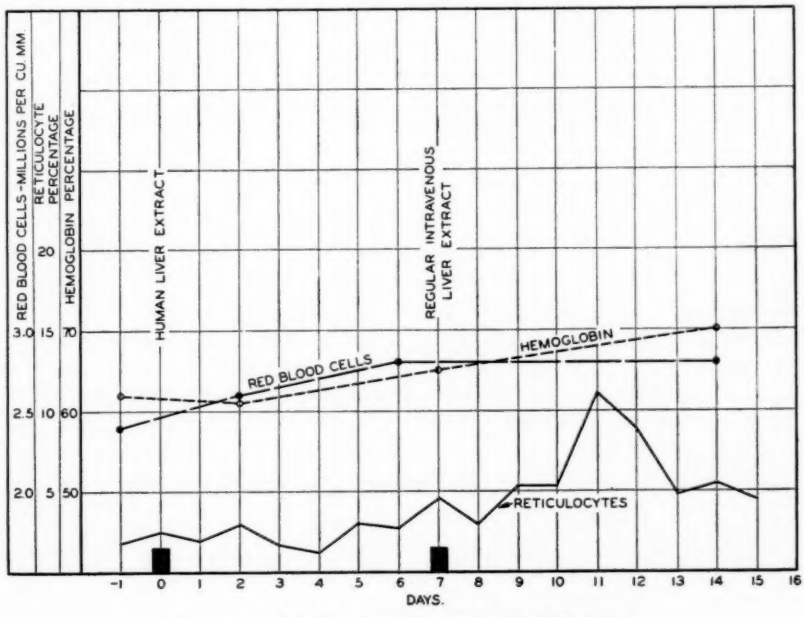

CHART 4.—Failure of response from cirrhotic liver.

its symptoms. It has not been possible to follow the second patient as he has not returned.

The Inability to Utilize the Active Principle, Even Though It is Stored, Suggesting a Fifth Factor in the Production of a Macrocytic Anemia. Experiment VI. An intravenous extract was made from the liver of a patient who had had acute yellow atrophy. On admission his red cell count was 2,450,000 per cmm.; hemoglobin, 54% (Sahli); 51% of the red cells were larger than 7.5 microns. When the parenteral extract prepared from this liver was given to a patient with pernicious anemia (red blood cell count, 1,530,000 per cmm.; hemoglobin, 41% (Sahli)), a maximum reticulocyte response of 34.6% was produced.

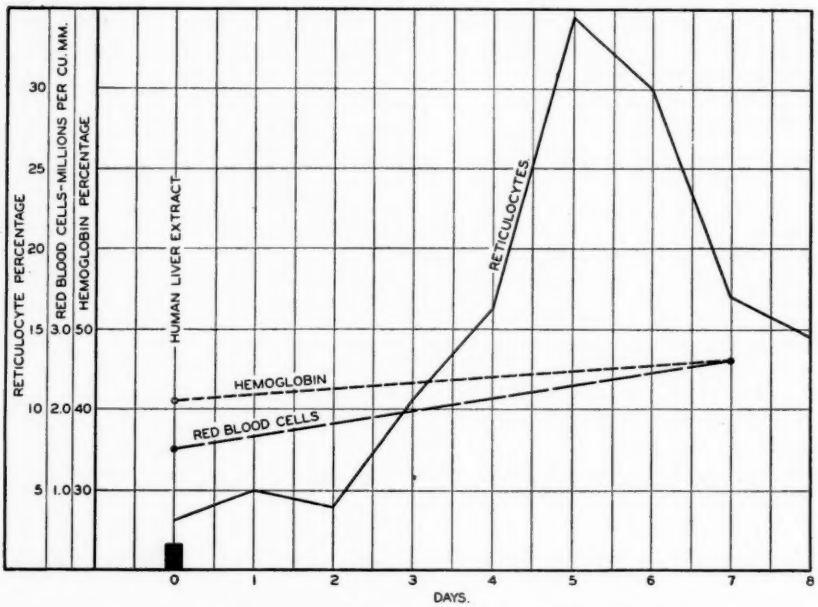

CHART 5.—Liver damaged from acute yellow atrophy—effective.

Although the unknown substance was present in the acutely damaged liver, for some unknown reason the patient with the acute yellow atrophy probably was unable to utilize it, as was evidenced by the severe macrocytic anemia which was present. This disturbance of metabolism by the liver is to be differentiated from the inability of storage as suggested in Experiment IV. (Chart 5.)

Discussion. From the above experiments, as well as those previously described by other authors,[3, 10] it can be concluded that liver tissue is primarily a storehouse for the hematopoietic substance necessary for the maturation of red cells. It is also highly suggestive that, although the active principle may be present in the liver, if sufficient hepatic damage is present, this organ is unable to release the necessary substance for red cell development in a suit-

able form for utilization by the body tissues. Thus, if for any reason, there is marked injury to the liver (cirrhosis, acute yellow atrophy), the normal hematopoietic rôle of the liver is disturbed and a macrocytic anemia may develop, though the stomach may make the necessary material.[10] This resulting blood picture may be clouded by a so-called "secondary anemia" with a low color index, due to gastro-intestinal bleeding. As previously mentioned, the macrocytic anemias, associated with cirrhosis of the liver, have been controlled by parenteral liver extract.[9, 10] Recently, Cheney[8] has suggested the use of "secondary anemia" liver extract and iron in the treatment of similar cases.

Conclusions. 1. The active principle necessary for the maturation of red cells is present in the liver at least 2 months before birth.

2. The active principle may be absent from the liver of an inadequately treated case of pernicious anemia.

3. The active principle is present in the liver of an adequately treated case of pernicious anemia.

4. A cirrhotic liver may not contain the active principle.

5. It is highly suggestive that a liver may be sufficiently damaged so that the active principle, though present, cannot be presented to the tissues for utilization.

6. A pernicious anemia-like blood picture may be present in a patient, if the liver is so damaged that it cannot store the active principle, or cannot present it to the body tissues in the proper form for utilization.

7. The demonstration that all livers do not contain the "active principle" indicates that it is a storage product rather than an intrinsic part of the liver substance.

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THE RELATION BETWEEN DEFICIENCY OF SOLAR RADIATION AND MORTALITY DUE TO PERNICIOUS ANEMIA IN THE UNITED STATES.

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The purpose of this article is to compare the amount of solar radiation with the mortality due to pernicious anemia in the states of the United States.

I. The total radiation received on a unit of horizontal surface from the sun and sky has been measured for 17 stations.[1] Kimball's report shows: (*a*) The annual march of daily totals of radiation, and (*b*) the average annual amounts of solar thermal energy received at these stations. The values are expressed as kilowatt-hours per square dekameter of horizontal surface. The stations for which climatic data are available for comparison with the measurements referred to, with a view to arriving at an index applicable to all weather bureau stations in the United States, are Madison, Wis., Lincoln, Neb., Washington, D. C., and Havana, Cuba. From Kimball's tables and reading from his charts, the measured data are shown in Table 1 (*a*). The data selected for comparison are shown in Table 1 (*b*). In this table a radiation index is calculated by dividing by 3 the sum of the angle of incidence of the sun's rays, the percentage of possible sunshine[2] and 100 minus the P.M. mean relative humidity.[2] One unit of this index is roughly equivalent to 3150 kw.-hr. per sq. dkm. *per annum* for the 3 United States stations.*

Chart I shows the correlation between the measured amounts of solar energy and the radiation index. The comparison appears to show a fairly close approximation and to warrant the use of the radiation index, so calculated, for the purpose at hand.

II. The average annual death rate from pernicious anemia per 100,000 estimated population in the registration area of the United States for the years 1921 to 1926 inclusive (prior to the therapeutic use of liver) is shown by states in Table 2[3] and is traced in Chart II. In comparison, Chart II shows also the radiation index for the corresponding states calculated as described above. The average of all stations reporting is used to compute the percentage of possible sunshine and the relative humidity for each state. From this comparison the following general statements may be made: The death rate from pernicious anemia is high in proportion to the radiation index in the western states with high altitude, high radiation index and relatively low latitude; the death rate is low in proportion to

* Madison 3171, Lincoln 3197, Washington 3117, Havana 3500. Figures for sunshine at Havana were not available and those for Key West, Florida, were used instead.

TABLE 1.—SOLAR ENERGY PER UNIT OF HORIZONTAL SURFACE.

TABLE 1.—SOLAR ENERGY PER UNIT OF HORIZONTAL SURFACE.

(*a*) Measured Values (After Kimball).

	Latitude. N ° ′	Longitude. W ° ′	Altitude. Meters	Kilowatt-hours per square dekameter. Daily mean. J	F	M	A	M	J	J	A	S	O	N	D	Annual.
Madison	43 05	89 23	308	192	277	362	451	541	603	588	500	389	268	173	146	139,523
Lincoln	40 50	96 41	381	243	340	435	507	577	654	653	569	462	343	247	203	160,906
Washington	38 56	77 05	137	194	276	376	467	544	572	548	498	424	332	225	169	145,493
Havana	23 09	82 21	40	374	457	569	613	587	618	637	565	507	425	341	333	184,488

(*b*) Index for Comparison with Measured Values.

Madison:													
A—Angle of incidence of sun's rays	30	38	46	54	62	70	62	54	46	38	30	23*	46†
S—Percentage of possible sunshine	43	52	55	53	57	64	69	64	58	50	42	38	54
H—100 minus 8 P.M. mean relative humidity	21	25	31	39	40	35	40	37	32	33	28	21	32
R—Radiation index $\frac{(A+S+H)}{3}$	31.3	38.3	44.0	48.7	53.0	56.3	57.0	51.7	45.3	40.3	33.3	27.3	44.0
Lincoln:													
A—	32	40	48	56	64	72	64	56	48	40	32	25	48
S—	57	59	62	59	62	72	76	72	63	61	58	54	63
H— (7 P.M.)	29	32	42	48	45	45	48	44	42	43	37	29	40
R—	39.3	43.7	50.7	54.3	57.0	63.0	62.7	57.3	51.0	48.0	42.3	36.0	50.33
Washington:													
A—	34	42	50	58	66	74	66	58	50	42	34	27	50
S—	47	54	55	58	61	62	64	61	64	61	55	49	58
H— (8 P.M.)	33	37	39	42	42	30	29	26	24	28	34	34	32
R—	38	44.3	48.0	52.7	56.3	55.3	53.0	48.3	46.0	43.7	41.0	36.7	46.67
Havana:													
A—	50	58	66	74	82	90	82	74	66	58	50	43	66
S— (Key West)‡	68	74	77	79	74	67	68	70	62	60	66	66	69
H— (8 P.M.)	23	24	27	27	24	20	22	21	19	21	22	23	23
R—	47.0	52.0	56.7	60.0	60.0	59.0	57.3	55.0	49.0	46.3	46.0	44.0	52.67

* Approximate.

† At equinox.

‡ Figures from Havana not available.

TABLE 2.—RADIATION INDEX AND MORTALITY DUE TO PERNICIOUS ANEMIA, BY STATES.

Radiation Index Above 51.

States.	Lat.	Alt.	Rad. Ind.	Minus Lat. subtracted from 49.	Corrected Rad. index.	P. A. mortality.	Comments.
GROUP A. (States in order of ascending latitude)	Latitude below 42.	(Group A, correction for excess index.)					
Arizona	34	2700	68.0	15.0	53.0	2.7	Altitude: Mean of stations reporting. Mortality from pernicious anemia per 100,000 estimated population 1921–1926 inclusive.
California	37 30	520	54.2	11.5	42.7	7.5	
Kansas	38 30	1700	53.8	10.5	43.3	6.9	
Colorado	39	4800	59.3	10.0	49.3	6.0	
Utah	39 30	4850	58.8	9.5	49.3	5.0	
Nebraska	41 30	1870	51.2	7.5	43.7	6.9	
GROUP B. (States in order of descending altitude)	Latitude above 42. (Group B, no correction.)						
Wyoming	43	5350	52.6	....	....	2.8	
Idaho	44	3550	55.3	....	....	3.0	
	Radiation Index Below 51. Altitude 3000 to 520 feet. (Group B, no correction.)						
Montana	47	2950	46.6	....	....	4.3	
North Dakota	47 30	1600	45.5	....	....	5.6	
Oregon	44	1330	46.6	....	....	6.6	
Minnesota	46	970	43.0	....	....	9.7	
Missouri	38 30	860	49.5	....	....	4.7	
Iowa	42	800	46.6	....	....	10.4	Iowa: The instance of greatest discrepancy between radiation index and mortality from pernicious anemia.
Vermont	44	800	37.7	....	....	9.2	
New Hampshire	44	800	37.7	....	....	9.4	New Hampshire: Climatic data estimated. See Vermont.
Wisconsin	45	700	44.3	....	....	9.0	
Kentucky	37 30	700	48.8	....	....	2.8	
Ohio	40 30	680	45.5	....	....	6.0	
Michigan	44 30	640	40.2	....	....	9.7	
Indiana	40	640	47.3	....	....	6.4	
Tennessee	36	600	49.3	....	....	2.8	
Illinois	40	520	47.3	....	....	6.2	

	Lat.	Alt.	Rad. Ind.	Plus Lat. subtracted from 49.	Corrected Rad. index.	P. A. mortality.	
GROUP A REVERSED.							
West Virginia	38 30	1250	41.5	10.5	52.0	3.5	Unique in low percentage of sunshine and high humidity for altitude (1250 feet) of reporting stations. It is treated like Group A except that the correction is an addition rather than a subtraction.
	Lat.	Alt.	Rad. Ind.	Plus 2 + Alt. in terms of 100 ft.	Corrected Rad. index.	P. A. mortality.	
GROUP C. (States in order of descending altitude)	Altitude below 520 feet. (Group C, addition for altitude.)						
Virginia	37 30	516	45.5	7.0	52.5	2.5	Virginia: Altitude includes Washington, D. C.
Pennsylvania	41	500	44.0	7.0	51.0	4.7	
Washington	47 30	450	39.8	6.5	46.3	6.3	
New York	43	380	41.3	5.8	47.1	5.5	
Georgia	33	340	50.3	5.4	55.7	1.4	
Alabama	33	300	49.7	5.0	54.7	1.2	
Mississippi	33	250	50.7	4.5	55.2	1.0	
North Carolina	35 30	250	48.5	4.5	53.0	1.6	
South Carolina	34	150	49.7	3.5	53.2	1.2	
Louisiana	31	100	49.6	3.0	52.6	1.7	
Maryland	39	100	47.7	3.0	50.7	3.7	
Delaware	39	100	47.0	3.0	50.0	3.8	Delaware: Climatic data estimated; see Maryland.
Connecticut	41 30	100	44.5	3.0	47.5	5.3	
Maine	45	50	40.7	2.5	43.2	7.7	
Massachusetts	42 30	50	42.5	2.5	45.0	7.3	
Rhode Island	41 30	50	42.2	2.5	44.7	5.9	
New Jersey	40	50	45.3	2.5	47.8	4.3	
Florida	29	0	49.7	2.0	51.7	3.8	
District Columbia	39	100	47.0	3.0	50.0	5.6	D. C. urban area.

the radiation index in the eastern and southern states with relatively low radiation index and low altitude; and the death rate is neither high nor low in proportion to the radiation index in the central states with altitude neither high nor low. These variations may represent either the inaccuracy of the index or an effect of altitude in increasing the death rate from pernicious anemia. There are recognized physiologic responses of the blood to increased altitudes, including increased number of red blood cells.

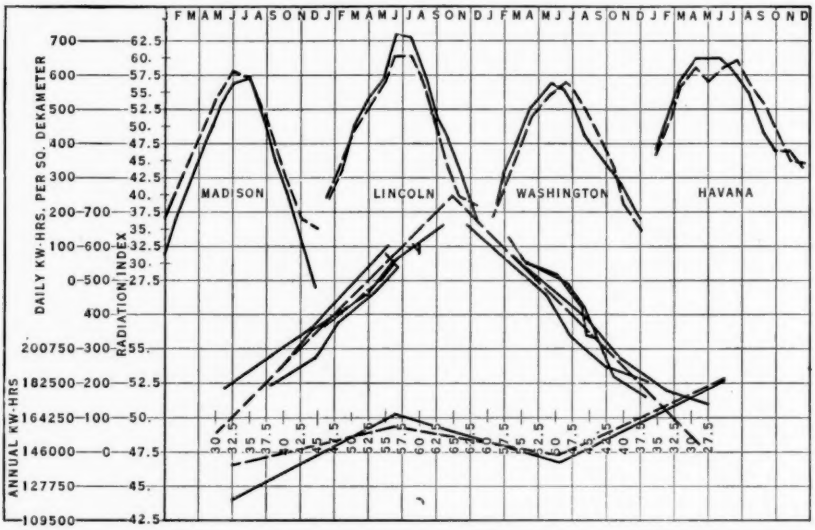
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
DAILY KW-HRS. PER SQ. DEKAMETER
RADIATION INDEX
ANNUAL KW-HRS
MADISON
LINCOLN
WASHINGTON
HAVANA

CHART I.—The upper series of 4 pairs of curves shows approximately the monthly march of mean daily totals of radiation received on a horizontal surface directly from the sun and diffusely from the sky, broken line (after Kimball) and the radiation index, continuous line, calculated for each month as described in the text. The central group of curves shows the same data plotted as a scatter diagram with the monthly points for each station connected by a solid line. The mean standard is represented by a broken line. The lower pair of curves represents the comparison between annual measurements (broken line) and the radiation index (continuous line) for each of the 4 stations.

The curve of corrected radiation index shown in Chart II is according to the principles embodied in Table 2. Since the corrections are on the basis of latitude and altitude, it would seem that they can be made in conformity with the concept of the index. However, with reference to either the uncorrected or the corrected index, comparison of states with each other within the 3 chief groups would seem to show a significant correlation between deficiency of solar radiation and mortality due to pernicious anemia.

Conclusions. 1. For the geographic and climatic conditions represented by Madison, Wis., Lincoln, Neb., and Washington, D. C., in the United States, and Havana, Cuba, the solar energy received per month and *per annum* is represented with fair accuracy by the

result of dividing by 3 the sum of the angle of incidence of the sun's rays at the equinox, the percentage of possible sunshine and 100 minus the mean relative humidity at about 8 P.M.

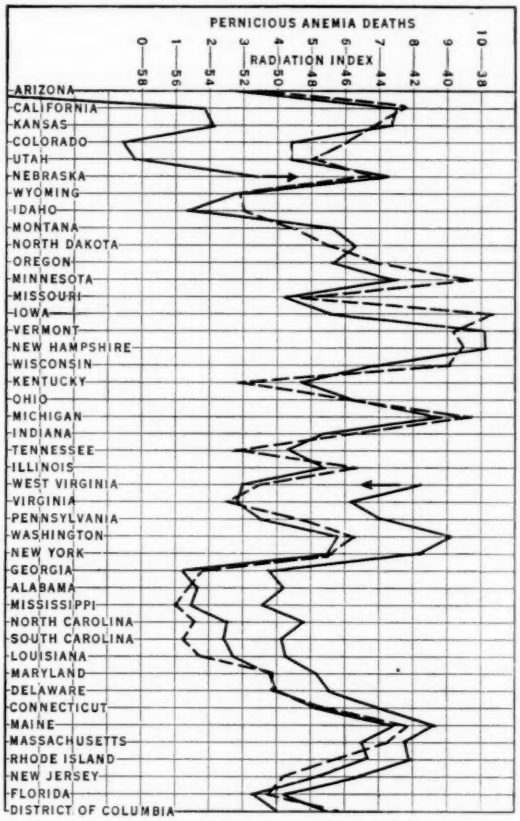

CHART II.—The scale for radiation index is reversed to make a low index comparable with height on the scale of mortality from pernicious anemia. The broken line indicates mortality from pernicious anemia, the continuous lines indicate radiation index. The curve of radiation index is uncorrected between the two arrows and on the left below and on the right above. Where it is continuous with the central portion it is corrected in its range to left and right of arrows as shown in Table 2.

2. The data presented are considered to show a significant relationship between relative lack of solar radiation and mortality from pernicious anemia in the United States prior to the introduction of the therapeutic use of liver.

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BILE PIGMENT AND HEMOGLOBIN REGENERATION.

THE EFFECT OF BILE PIGMENT IN CASES OF CHRONIC HYPOCHROMIC ANEMIA.*

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NUMEROUS investigators have studied the problem of pigment metabolism and debated whether any of the bile pigment that flows into the intestine is conserved by absorption for some purpose associated with hemoglobin regeneration. There is no definite agreement as to whether or not bile pigment can be absorbed and utilized by the body for this purpose. The studies have been made largely on animals and not on patients with anemia. From experimental work with bile-fistula dogs, Whipple[1] and his coworkers conclude that bile pigment is a waste product. By injecting hemoglobin or by feeding bile[3,4] to dogs in good nutritional condition but rendered anemic by chronic blood loss, a failure to gain in hemoglobin and a recovery of the bile pigment indicated that pigment was not conserved. Although Blankenhorn[6] and other investigators[7] found that, in dogs, bilirubin as such is not absorbed from the intestine, they have indicated that other bile pigments may be taken into the body from the intestinal tract. The studies of Broun, McMaster and Rous[8] and other observers[9,10] support the contention that bile pigment can be absorbed from the intestine for building hemoglobin. The former authors showed that after feeding sheep bile to dogs it could be recovered in the dogs' bile. Furthermore, it has been demonstrated in animals that chlorophyll[11,12] and related pyrrol substances[13] can be absorbed so as to influence favorably the regeneration of hemoglobin.

Ever since Virchow[14] identified the chemical similarity between hematoidin and bilirubin in blood extravasations, there has been an implied interrelationship between hemoglobin and bile pigment metabolism. Where blood destruction is prominent as in hemolytic jaundice, it is well recognized that the increased excretion of bile

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pigment is due largely to the rapid liberation of hemoglobin from the red cells. An increased excretion of bile pigment, as in pernicious anemia, may depend in part upon an inability of the body to utilize pigment-forming substances, not necessarily derived from excessive red blood cell breakdown. Studies, which are less widely appreciated, indicate that the amount of bile excretion is diminished by blood loss and conversely that loss of bile through fistula may result in anemia. For example, Whipple[2] has shown that dogs rendered anemic by repeated hemorrhage excreted less bile than normal dogs. McMaster, Broun and Rous[15] and Seyderhelm[16] note that dogs with biliary fistulæ, and presumably without bartonella infection, develop anemia, although Whipple does not concur in these findings. There has been disagreement as to the technique, results, and interpretation, but in the final analysis it seems likely that an interplay of some sort occurs between the factors for hemoglobin formation and bile pigments. It is not implied that because hemoglobin is a precursor of bile pigment, the reverse must take place, but it is felt, in view of studies to be described, that bile pigment probably plays a rôle in hemoglobin formation.

It would be hazardous to make literal translation to human disease of evidence coming solely from the unnatural conditions imposed by animal studies. In addition to the experimental data, however, there is clinical evidence supporting the hypothesis that bile pigment may be concerned in hemoglobin formation. Decreased pigment content of the plasma in "secondary anemia" has been known for a long time. As Whipple[17] says: "Secondary anemia in direct contrast to pernicious anemia is a disease in which there is a deficit of hemoglobin pigment and related pigments." The low icteric index of uncomplicated cases of hypochromic anemia stressed by Meulengracht,[18] and the decreased bile pigment excretion in the stools as noted, for example, by Addis[19] imply a pigment want in these patients.

The oral administration of adequate amounts of inorganic iron can cause rapid hemoglobin regeneration in many patients with hypochromic anemia. Iron given parenterally[20] may be recovered in the blood almost quantitatively in an organized form—hemoglobin; but as the hemoglobin rises, there tends to be a greater discrepancy between the amount of iron injected and the amount of hemoglobin formed. Iron cannot, of course, by itself make hemoglobin. Copper, and apparently other mineral elements,[21,22,23] may supplement the effectiveness of iron in rats rendered anemic by milk diet; but something more than minerals is required to form the complex hemoglobin molecule. Certain amino acids may affect hemoglobin regeneration,[24] and a deficiency of these might play a rôle in disease, so that a proper supply might facilitate the building of a portion of the hemoglobin molecule. In hypochromic anemia where iron is so effective, the body may perhaps retain a sufficient

supply of factors other than iron from which to make hemoglobin. However, it is reasonable to suppose that in some cases these factors, too, are deficient; or if they are not actually deficient, perhaps an inability to utilize them may exist. Theoretically, also, some abnormality in the utilization of iron may occur which might be overcome when a suitable supply of other hemoglobin-building substances is made available.

In chronic hypochromic anemia there is often more than one etiologic factor; dietary deficiency, faulty gastro-intestinal function, including achlorhydria, blood loss and pregnancy—all may play a rôle in causation. Thus, there are numerous opportunities for deficiencies in the body of other material than iron necessary for the synthesis of hemoglobin.

With adequate iron therapy certain patients with hypochromic anemia are unable to reach or maintain a hemoglobin concentration of more than about 75% of normal, when evidence of inhibitory factors, such as infection, is lacking. Occasionally in such cases, the addition of liver, rich in pigment pyrrols, satisfies the gap.[25,26] Whipple[17] has shown clearly that liver harbors material which independently of iron, is potent for blood regeneration in hypochromic anemia due to hemorrhage. This substance is different from the substance in liver effective for pernicious anemia.

Presumably factors for the construction of the globin portion of hemoglobin are contained in any diet that is not lacking in suitable protein, and perhaps the same may be true for the hematin portion—a pigment pyrrol component. There is indirect evidence, however, that this portion is more necessary to the body economy. Since bile pigment is diminished in cases of hypochromic anemia and since it is rich in the hemopyrrol material found in hemoglobin, it was decided to determine what hemopoietic effect, if any, concentrated bile pigment might exert in human chronic hypochromic anemia. These cases are most satisfactory ones in which to estimate the value of material for hemoglobin regeneration. This is not only because of the relatively much greater reduction of hemoglobin than red blood cells, but also because such cases do not develop "spontaneous" improvement in their blood, except occasionally, and then only very slowly.

Methods. Reticulocyte counts were made daily on capillary blood. Hemoglobin and red blood cell counts were determined from venous blood every 2 or 3 days. The hemoglobin was estimated from an average of two readings with Sahli hemometers, standardized by van Slyke oxygen capacity determinations, so that 15.6 gm. of hemoglobin per 100 cc. corresponded to a capacity of 21 volumes of oxygen %.

Before the observations reported here on the effects of concentrated bile pigment were begun, the same sort of observations were made with ox bile (*fels bovis*, U. S. P.) on 6 cases of chronic hypochromic anemia. When about 2 gm. daily were given, responses of the same sort as reported below were obtained, but their magnitude was slight. This amount of

fels bovis often caused epigastric distress and diarrhea, presumably from the bile salts. Diarrhea, of course, could prevent absorption and lead to dehydration, thus confusing hemoglobin values. Therefore, a preparation relatively free from salts was sought after, for it was believed that the hemopoietic effect noted had been due to pigment rather than bile salts, as claimed by Seyderhelm.[27] Eli Lilly and Company kindly made the concentrated preparation of bile pigment used by a process briefly described as follows: Beef bile was made alkalin with ammonium hydroxid and a concentrated solution of calcium chlorid added to the point of complete precipitation. The precipitate was centrifuged off and washed with water, 10% acetic acid, a mixture of acetone and ether, and ether. The residue was then dried quickly *in vacuo*. This provides a product essentially free of bile salts, inorganic salts, cholesterol, fats and mucin. On chemical analysis only traces of iron were present.

The pigment was administered in capsule form because of its bitterness. No toxic or undesirable effects took place.

Nine selected cases of chronic hypochromic anemia were fed the concentrate of bile pigment. The first 8 cases had not been treated. The patients were given the usual hospital fare, excepting meat and eggs. After about 5 days' observation, during which time the blood values were unaltered, each patient was given daily about 2 gm. of the bile pigment for an average of 6 days. No other medication was used until a 10-day period had been fulfilled.

A second period of 10 days followed directly, during which iron and ammonium citrate was given in daily doses, usually of 0.5 gm. In a third period the same daily dose of iron was continued, and in addition bile pigment in about the same amount as before. Thus, there were 3 sets of observations, namely, on the effects of bile pigment, on small doses of iron, and on iron with bile pigment. All medication was given by mouth and the same vehicle, either milk or orange juice, was used throughout the observations on the one case. Two sets of observations were also made on the effect of bile pigment in a patient (Case 9) with idiopathic hypochromic anemia, who had been unable to regain a normal hemoglobin level in spite of large doses of iron for many months.

Results. Table 1 records synoptically the observations on the effect of bile pigment, iron, and iron with bile pigment successively. It is emphasized that this tabulation begins after an observation period without therapy when the reticulocytes and hemoglobin remained remarkably constant. In the first period with bile pigment there occurred a rise of hemoglobin unaccompanied by a change in the reticulocytes. The hemoglobin rise in 10 days was usually about 6%, and in Case 4 was 15%.

The second period with a distinctly suboptimal daily dose of iron and ammonium citrate follows directly; that is to say, the second day of this period was 2 days after the last observation recorded in Period 1. The only notable effect here is that with considerable regularity, there occurred a small reticulocyte response, although in Case 2 a relatively rapid and large response took place. During this period the hemoglobin concentration in each case, except Case 2, remained practically constant for 10 days. In Case 2, with the unusually pronounced reticulocyte response to a small dose of iron, the hemoglobin rose 10% between the 10th and 20th days.

TABLE 1.—THE ORAL ADMINISTRATION TO 8 CASES OF HYPOCHROMIC ANEMIA OF FIRST, BILE PIGMENT; SECOND, IRON AND AMMONIUM CITRATE; AND THIRD, A COMBINATION OF THESE TWO.

Bile Pigment Alone.

	2.2 gm. daily for 5 days.		2.0 gm. daily for 5 days.		2.0 gm. daily for 5 days.		2.0 gm. daily for 5 days.		1.2 gm. daily for 7 days.				2.0 gm. daily for 7 days.		2.5 gm. daily for 7 days.	
	Case 1.		Case 2.		Case 3.		Case 4.		Case 5.		Case 6.		Case 7.		Case 8.	
Days of treatment.	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %	Hgb. %	Retics. %
0	48	1.1	40	1.1	64	0.9	44	1.1	45	0.8	..	...	42	0.8	40	0.5
2	49	1.7	43	0.8	65	0.7	46	0.8	45	0.6	..	...	42	0.9	42	0.6
4	54	1.4	43	0.9	67	0.7	50	1.1	45	1.2	..	...	44	1.2	42	0.4
6	56	1.1	42	1.8	68	1.0	52	0.8	46	0.8	..	...	45	1.1	44	0.6
8	56	1.0	46	1.1	69	1.2	52	0.9	48	0.4	..	...	45	1.1	46	1.0
10	..	...	48	1.7	70	0.7	59	0.9	50	0.5	..	...	46	1.2	46	1.1

Iron and Ammonium Citrate Alone.

	0.4 gm. daily.		0.5 gm. daily.				0.4 gm. daily.		0.4 gm. daily.		0.75 gm. daily.		0.5 gm. daily.		0.6 gm. daily.	
2	55	1.9	48	7.3	..	...	59	0.6	50	0.5	32	0.9	46	1.3	46	0.9
4	56	2.0	49	9.9	..	...	58	1.6	50	1.1	33	0.8	45	1.4	45	1.7
6	55	0.7	49	5.6	..	...	56	2.0	49	3.3	32	3.4	45	2.2	47	1.6
8	55	0.9	50	4.1	..	...	56	3.5	48	1.9	33	1.9	45	2.5	48	0.7
10	..	...	50	3.0	..	...	55	1.0	48	2.1	35	0.8	..	3.4	46	1.2
12	..	...	51	5.0	..	...	58	1.3	..	...	..	...	45	2.0	..	...
14	..	...	58	3.0	..	...	58	1.0	..	...	..	...	..	...	..	...
16	..	...	58	4.2	..	...	57	1.1	..	...	..	...	..	...	..	...
18	..	...	58	3.3	..	...	56	1.3	..	...	..	...	..	...	..	...
20	..	...	60	3.0	..	...	56	1.1	..	...	..	...	..	...	..	...
22	..	...	..	...	..	...	58	1.5	..	...	..	...	..	...	..	...
24	..	...	..	...	..	...	58	1.7	..	...	..	...	..	...	..	...

Iron as Above Plus Bile Pigment.

	2.2 gm. daily for 6 days.		2.0 gm. daily for 6 days.				2.6 gm. daily for 6 days.		1.3 gm. daily for 6 days.		2.0 gm. daily for 4 days.		2.8 gm. daily for 7 days.		2.5 gm. daily for 7 days.	
2	54	1.3	60	3.8	..	...	57	1.7	48	1.9	35	0.8	44	1.6	46	0.9
4	55	4.9	60	6.6	..	...	58	1.5	48	1.0	36	1.3	45	3.5	46	2.0
6	58	2.2	60	13.0	..	...	58	3.1	49	0.8	37	3.2	48	6.4	46	3.2
8	61	1.4	65	7.8	..	...	59	1.8	48	1.1	38	...	50	2.5	44	1.3
10	60	0.9	65	1.5	..	...	59	1.1	48	...	38	1.2	55	1.1	46	...
12	..	...	..	...	..	...	60	1.1	..	...	..	...	..	...	..	...
14	..	...	..	...	..	...	62	1.3	..	...	..	...	..	...	..	...

NOTE.—The red blood cell counts are not recorded. Their numbers were essentially unchanged during the observations. The average initial level was 4,000,000 per cmm. The most marked change occurred in Case 2 (*Cf.* Chart II). For the sake of brevity only the bi-daily data are recorded. The periods are consecutive. For example, the second day of the second period is 2 days after the last observation for the first period.

In the third period in which bile pigment was added, and the same dose of iron maintained, a second reticulocytosis took place with regularity, except in Case 5, which was given only 65% of the

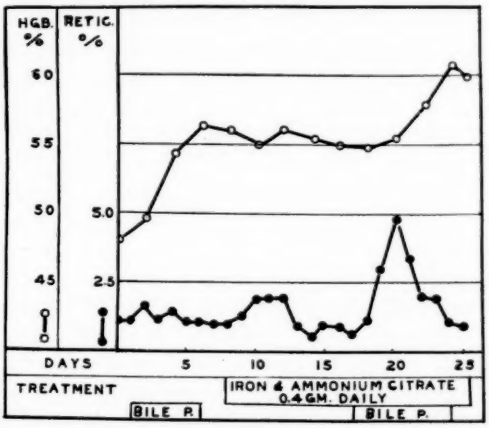

CHART I.—Hemoglobin and reticulocyte responses to the feeding of bile pigment and iron in a patient (Case 1) with chronic hypochromic anemia. This chart is scaled to illustrate clearly the effects on hemoglobin.

amount of bile pigment administered to any other case. The hemoglobin concentration increased 5% in 10 days on the average

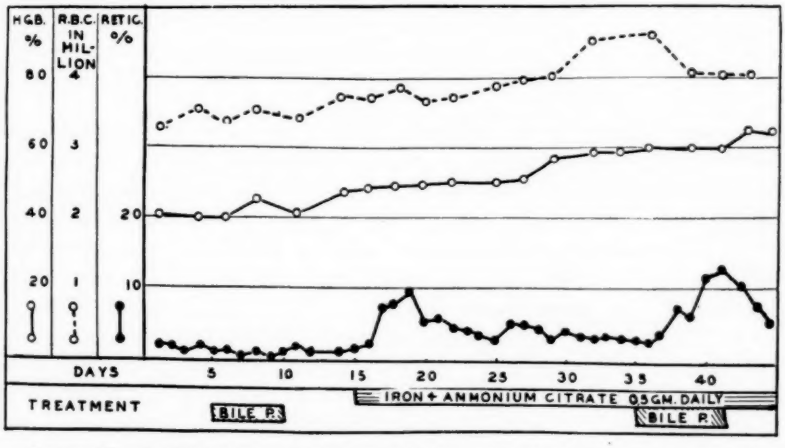

CHART II.—Red blood corpuscle, hemoglobin and reticulocyte responses to the feeding of bile pigment and iron in a patient (Case 2) with chronic hypochromic anemia.

for 5 cases, but in the other 2 cases (Nos. 5 and 8) the hemoglobin remained constant.

In all instances after these observations had been made, 6 gm. of

NOTE.—The red blood cell counts are not recorded. Their numbers were essentially unchanged during the observations. The average initial level was 4,000,000 per cmm. The most marked change occurred in Case 2 (*Cf.* Chart II). For the sake of brevity only the bi-daily data are recorded. The periods are consecutive. For example, the second day of the second period is 2 days after the last observation for the first period.

iron and ammonium citrate were given daily and the hemoglobin rose rapidly. In Charts I and II there is a graphic representation of the data for 2 of the cases (Nos. 1 and 2) which permits one to observe more readily than from the table the course of events.

In Table 2 are recorded synoptic data concerning a woman with severe idiopathic hypochromic anemia and achlorhydria (Case 9)

TABLE 2.—THE EFFECT OF FEEDING BILE PIGMENT IN A CASE (NO. 9) WHICH DID NOT OBTAIN A NORMAL HEMOGLOBIN LEVEL WHEN TREATED FOR MONTHS WITH 6 GRAMS OF IRON AND AMMONIUM CITRATE DAILY. (Synoptic Data.)

Duration.	Hemoglobin per cent.	R. B. C. millions per cmm.	Therapy daily.
Anemic 15 years . . .	15	2.0	None.
After 3 months	70	4.0	Iron.
For 7 months	68–73	3.7–4.0	Iron.
For 4 months	71–73	3.8–4.0	Iron + 4 gm. Vegex.
After 2 days	71	3.9	Iron + 1 gm. bile pigment.
After 4 days	76	4.0	Same.
After 8 days	76	3.8	Same.
After 10 days	80	4.2	Same.
After 12 days	81	3.9	Same.
After 16 days	85	4.2	Same.
After 15 days	78	4.0	Iron.
After 30 days	76	4.4	Iron.
After 130 days	74	4.3	Iron.
After 30 days	81	4.3	Iron + 1 gm. bile pigment.
After 65 days	73	4.0	Iron.

who had been unable to regain a normal hemoglobin level in spite of large doses of iron. This patient, a 62-year-old widow, had been anemic for 15 years. For a long time her diet had contained little animal food, except milk and butter, and only small amounts of puréed vegetables and fruit. She suffered also from dysphagia and, although this symptom decreased greatly in severity as the hemoglobin concentration increased from 15 to 70% with iron therapy, it prevented her from being willing to take a well-balanced diet. Thus, not only while under treatment for 22 months but for years previously, her diet had been deficient in various ways. Throughout the observations she took 6 gm. of iron and ammonium citrate daily. In the 11 months before bile pigment was given, the constancy of her hemoglobin concentration, about 70%, was remarkable. The rise to 85% in 16 days, when 1 gm. daily of the bile pigment preparation was added, thus seems significant. On discontinuing pigment for 4 months the hemoglobin slowly fell to 74%. Upon resuming the bile pigment again for a month the hemoglobin rose to 81% and fell once more in about 2 months to 73% with iron alone.

This patient was also given a concentrate of vitamin B (Vegex) 4 gm. a day for 4 months to see if it could affect her hemoglobin, but it did not do so.

Discussion. The changes in the percentage figures for reticulocytes recorded with the data synopsized in Table 1 may appear unimpressive to persons who are not acquainted with reticulocyte responses in hypochromic anemia. One should recognize that a 2% increase of reticulocytes in a red blood cell count of 4,000,000 per cmm. represents a total increment of 80,000 such cells per cmm., and that under the strict conditions of the experiments, the changes which occurred are of significant magnitude. A considerable regularity of the responses and a similarity of the patterns of response to bile pigment with and without iron in the different cases, indicate that coincidence or chance are not the cause of the blood changes observed. When bile pigment alone was fed, the increase of hemoglobin concentration, although slight, occurred without appreciable change in the number of reticulocytes or red blood cells. This suggests a special focus of effect, that the pigment was absorbed and was used in the construction of hemoglobin, as McMaster and Elman[9] and Zih[10] contend took place in their animal experiments.

The data presented do not indicate the extent of hemoglobin rise with protracted feeding of bile pigment alone. There is evidence at hand that in such cases hemoglobin will increase no more than the 8 patients showed, when pigment feeding is continued beyond about 10 days.

The suboptimal daily amounts of iron were given so that any effect on blood formation of adding bile pigment could be demonstrated by the course taken by the reticulocytes. If optimal daily doses of iron are given continuously, no further response of the reticulocytes occurs after the initial reaction subsides. It has been shown, however, that if a suboptimal quantity of potent material is given daily, and no reaction or a suboptimal reticulocyte response occurs, and that if then a second reaction takes place when material is added, the substance causing the second response is more potent than the first. If the second response is greater than the first, the potency of the material responsible for this reaction is greater than the material first tested.[28] The data recorded in Table 1 and Charts I and II, indicate the occurrence of a second reticulocyte reaction when bile pigment was added to daily suboptimal (0.5 gm.) doses of iron and ammonium citrate. Indeed, sometimes (Cases 2 and 7) this response was as great as that usually expected with optimal doses of iron and ammonium citrate for the given hemoglobin and red-cell level, as determined by Minot and Heath.[29] Differences in response could depend upon the anatomical and functional state of the gastrointestinal tract and hemopoietic organs of the given patient's body. In anemia in man, seldom will these factors be identical, as may occur in experimental animals.

The second reticulocyte reaction occurred a trifle earlier and more abruptly than after the response to 0.5 gm. iron and ammonium citrate alone. This also happens when a suboptimal amount of iron is replaced by an optimal dose. It is believed, therefore, that the bile pigment facilitated either iron absorption or utilization.

We have as yet not determined whether hemoglobin regeneration with bile pigment and small doses of iron will continue to the normal level at essentially the same rate, as occurred in some of the cases in a 10-day period.

Speculation on how bile pigment increases the effect of iron is interesting but will not be discussed. Many factors must be considered, such as the composition and state of the gastro-intestinal contents, the transfer of the material across its membranes, the intermediary agents of iron and hemoglobin metabolism.

There are several factors which may enter into the etiology of chronic hypochromic anemia. Justly, Robscheit-Robbins[30] has criticized the confusion arising out of failure to distinguish between nutritional anemias and blood-loss anemias; but in adult human cases one dare not be dogmatic about the exact condition in a given case. For instance, the patient with chronic blood loss usually develops a poor appetite and finally a dietary lack. Achlorhydria may hinder iron absorption or utilization. Menorrhagia and pregnancy also may intensify anemia in a woman who has had a faulty diet for years.

Such conditions may explain why man may respond and why Whipple's dogs[4,5] did not respond by increase of hemoglobin to pigments rich in hemopyrrol groups. The dogs with chronic blood loss were in good nutritional states, whereas the patient with hypochromic anemia whose diet characteristically is high in concentrated carbohydrate food and low in protein may need the factors supplied in the control "salmon bread" diet given to Whipple's dogs.

The observations we have recorded are regarded mostly as of physiologic interest because adequate amounts of iron alone alleviate hypochromic anemia in many patients. It is, of course, important for all individuals to have a proper diet. If the patient with hypochromic anemia persistently has a faulty diet, although iron can cause great improvement, the body may be deficient in other factors needed to make hemoglobin. It is suggested that such a condition occurred in the patient (Case 9) who could not obtain a normal hemoglobin level with large doses of iron. The prompt rise of hemoglobin following the feeding of bile pigment after a trial period of 1 year with iron cannot be considered fortuitous, especially when the same event took place a second time. Other cases of this sort should be observed, and determinations made as to whether bile pigment or other pigment substances sometimes may not be of therapeutic value.

Summary. Nine selected patients with chronic hypochromic anemia were studied to determine whether bile pigment could assist in hemoglobin production.

Concentrated bile pigment alone caused not a reticulocyte response but an increase of hemoglobin, about 7% in 10 days. This indicates that in certain anemic patients bile pigment can be absorbed from the gastro-intestinal tract for building hemoglobin.

After a reticulocyte response occurred to a suboptimal dose of iron, bile pigment was fed directly with the same dose of iron, and there followed a second reticulocyte response. The second response was sometimes of greater magnitude than the first. This indicates that bile pigment in some unknown manner can facilitate either iron absorption or utilization.

One patient who could not obtain in 14 months a normal hemoglobin level with large daily doses of iron promptly increased her hemoglobin concentration when bile pigment was fed in addition to iron.

It is suggested that in certain cases of hypochromic anemia there may be a deficiency of a useful material that is contained in bile pigment in addition to iron deficiency.

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NOTE ON INEFFECTIVE USE OF THEELIN IN A CASE OF HEMOPHILIA.

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The object in the treatment in hemophilia is twofold—to secure hemostasis during hemorrhage and to render the patient less susceptible to bleeding at all times. That there are numerous methods of treatment, renders all suspect. Various characteristics of the disease contribute to the difficulties of evaluation. As the patient becomes older, the tendency to bleed decreases. There is also a constantly changing tendency of a hemophiliac to bleed, and coagulation time tests made at different times may range from a normal clotting time to one which is markedly delayed. These changes may be abrupt and marked without apparent reason. It has been impossible, however, through therapeutic measures available to us, to lower the hemophiliac's clotting time, and to keep it low. The Spanish preparation, "nateina," for instance (containing vitamins A, B, C and D, with calcium phosphate and lactose), though in widespread favor in Europe at present, is not recommended by more recent studies.[1]

There has always been an attempt to link the sex-limited nature of this disease with some peculiarities in the sex glands or hormones. This offered a basis for study of the therapeutic value of the female sex hormone. In 1904, Grand and Heyter[2] administered female sex gland by mouth. Ten years later, Schlossman[3] repeated their attempts, all of which yielded unsatisfactory results. More recently, Birch[4, 5] studied the excretion of female sex hormone in the urine of hemophiliacs and hemophilia conductors. In normal male urine, minute quantities of female sex hormone is present. In hemophilic urine, no trace of this hormone could be found. With these facts as a basis, she transplanted whole ovary into the abdominal wall of a hemophilic boy and reported that he was free from bleeding for the entire period of observation (5 months). Subsequently she has resorted to the injection of female sex hormone, with apparently good results. During the past year, several reports in the literature speak favorably of this method.[6, 7] Mills[8] states that biweekly subcutaneous injections of 1 cc. theelin lowers the coagulation time of hemophilic blood. Larger doses, or less frequent injections, are of less favorable value.

For the past several months we have had an opportunity to study the effect of theelin on the bleeding tendencies of a hemophiliac. In addition to the clinical observations on the frequency, duration

and severity of bleeding, we followed the effect of treatment on the coagulation time. We felt that it was important to secure a lowering of the coagulation time, which would be persistent, before we could pronounce the treatment a therapeutic success. But it is necessary, in adhering to this criterion, to remember that hemophilic blood varies in its degree of coagulability spontaneously. Hence, observations must be made over long periods of time before results can be called conclusive.

Case Abstract. The patient, at present aged 26, first came under observation in 1926 with the history of repeated bleeding in childhood. His maternal uncle is a known bleeder, but no other history of hemophilia is available. During the 7 years of observation he has had numerous severe hemorrhages, many of spontaneous origin, many others following trauma. Hemorrhages have been most often into the gastro-intestinal tract, and into the left elbow and right shoulder joints. He has required numerous transfusions, and at times has been critically sick from exsanguination. From November, 1931, to November, 1932, he had 4 attacks of bleeding into the right shoulder joint. Bleeding, swelling, pain and limitation of motion during each attack lasted from 10 to 14 days. It was toward the end of an attack of hemarthrosis in October, 1932, that theelin therapy was begun. After the second dose of 1 cc., given on successive days, the bleeding stopped promptly. Since this was about 10 days after the onset of his illness, the usual duration of previous attacks, we were inclined to consider the circumstances of treatment and result as coincidental. On November 19, 1932, pain, swelling and the usual sequelæ appeared in the right shoulder. He received 4 daily injections of 1 cc. theelin intramuscularly from November 21 to 23. After the second injection, 4 days after onset, the pain was almost gone, and he was able to move his arm. By November 23, he was over this attack, in less than $\frac{1}{2}$ of his usual period of disability.

We planned, after the elapse of a sufficiently long period of time, so that the effects of the hormone would not interfere with our observations, to make clotting time determinations, institute theelin administration and study the effect of various doses on the coagulation time and on the prothrombin time. In a symptom-free period, December 6, the results of the blood studies were as follows: Red blood cells, 4,750,000; white blood cells, 7500; hemoglobin, 70% (Sahli); fragility normal; bleeding time, 3 min.; clotting time (Howell's method), 38 min.; prothrombin time, 32 min.; clot retraction time, within 12 hr. The only abnormal findings in these tests were prolonged coagulation and prothrombin time, the normal values of which are within 10 min.

Four daily injections of 1 cc. each were given, beginning December 6. Three days after the last injection, clotting time was 30 min.; prothrombin time, 7 min. Accordingly, confident that we had secured some results, we prescribed the oral preparation of female sex hormone, theelol, 1 capsule daily. The patient continued well until December 31, when he noticed headache, dizziness and sleepy spells, which in the past had accompanied bleeding. Coagulation time now was 40 min; red blood cells, 3,690,000; hemoglobin, 45% (Sahli), with considerable occult blood in the stool. He went to bed and received a daily injection of theelin for 4 days, the last one being given on January 3, 1933. On January 5, he felt much better, and the stool had a normal appearance. On January 6, coagulation time was 12 min.; prothrombin time, 18 min.; 1 cc. of theelin was also injected. Five days later the coagulation time was still 12 min. The dose was repeated, and after another interval, this time of a week, coagulation time

had increased to 31 min., prothrombin time to over 50 min. Another dose of 1 cc. was administered on this day, January 18. On January 23, the clotting time was 23 min., prothrombin time 50 min.

A series of 4 daily injections was begun on January 26. The clotting time changed from 23 min. to 17 after the 3d injection. Prothrombin time remained at about 1 hour. Three days after the last of this series of injections, clotting time was 24 min.

A second series of injections, this time 2 cc. daily for 4 doses, was begun on February 1. The clotting time remained virtually unchanged. Prothrombin time fluctuated markedly, but inconsistently during the period of treatment and not in consonance with the coagulation time.

The dose subsequently was reduced to 2 cc. every other day. This series began on February 6 and continued through February 20, for a total dosage of 16 cc. During this time the coagulation time fluctuated between 15 and 25 min. The prothrombin time varied from 18 to 25 min. On February 21, bleeding began in the right shoulder. On February 23, coagulation time had risen to 34 min., prothrombin time to 48 min. On this date, a daily injection of 1 cc. of theelin was begun. On February 24, the coagulation time was 30 min. On February 25, the pain in the shoulder was disappearing, the patient was again able to raise his arm. The coagulation time was 22 min. On February 27, the patient was quite well; coagulation time was 24 min., prothrombin time 30 min.

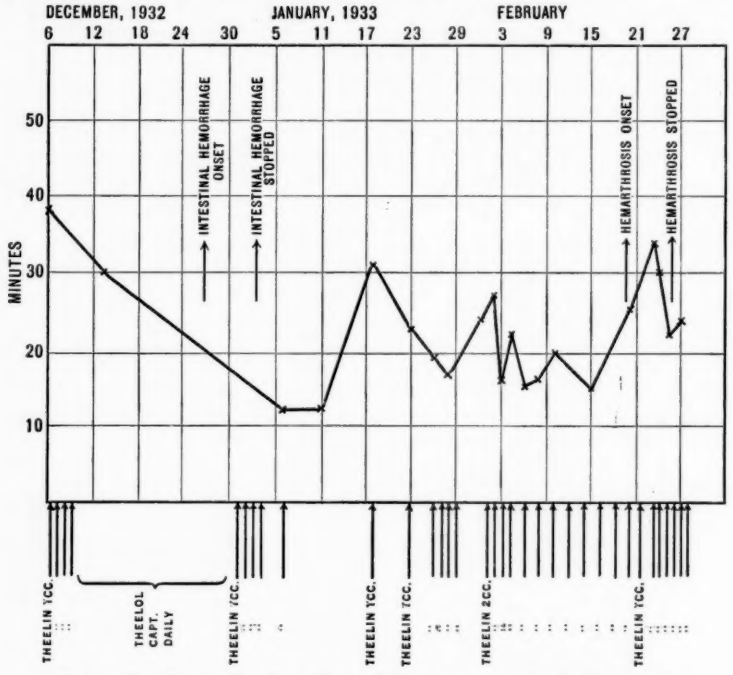

CHART I.—Curve showing effect of theelin upon coagulation time.

The accompanying chart is a summary of the treatment and the curve of the coagulation time. Although in the earlier days of observation, the clotting time seemed to decrease after the administration of theelin, and the bleeding stopped shortly after the insti-

tution of theelin treatment, twice during the course of treatment the patient developed spontaneous hemorrhages, once from the intestines and once into the shoulder joint. The coagulation time fluctuated markedly during January and February regardless of the dosage of theelin given. At no time were we able to bring the coagulation time down to a normal level, nor were we able to make any definite decrease in coagulation time, a persistent condition. Since cessation of regular theelin administration, the patient had an attack of hemarthrosis in April and a severe attack of gastro-intestinal bleeding in May. After 4 daily injections of theelin the hemarthrosis stopped. However, no clinical effect was obtained with theelin during his attack of intestinal hemorrhage.

Summary. Attempts to render a hemophilic individual less susceptible to bleeding by the use of the theelin, injected intramuscularly, or administered by mouth, have failed. We have been unable to observe a constant lowering of the coagulation time as a result of this treatment, nor has the coagulation time been reduced to a normal level during the period of observation. If theelin therapy is an effective remedy, we have as yet not learned the proper dosage and interval of administration.

I am indebted to Dr. Llewellyn Sale for the opportunity to study this case.

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ABDOMINAL DISEASE SIMULATING CORONARY OCCLUSION.

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Before coronary occlusion was described as a clinical entity,[1] cases of acute myocardial infarction were frequently misdiagnosed cholelithiasis, perforated peptic ulcer, or acute indigestion. Shortly after the clinical features of this condition were described, however,

a number of articles appeared in the literature reporting cases which at first appeared to be acute upper abdominal disease, but which ultimately proved to be acute coronary occlusion.[2-7] The differential diagnosis of coronary artery disease and upper abdominal disease has been adequately discussed.[3, 5-7]

More recently the knowledge of coronary occlusion has become so widespread that it is very frequently diagnosed. This diagnosis is usually made correctly, but occasionally erroneously. The result is that one now encounters cases of upper abdominal disease which have been erroneously diagnosed angina pectoris or coronary occlusion. In 1925 Robey[8] reported 2 cases of gall bladder disease in which some of the symptoms, especially precordial or substernal pain, suggested angina pectoris, and also 2 cases in which both gall bladder disease and coronary disease were present. He also discussed the differential diagnosis. In 1932 Brown[9] discussed atypical and referred pain due to visceral disease and pointed out that coronary disease may simulate upper abdominal disease. He also emphasized that cardiac symptoms may predominate in unsuspected gall bladder disease, and that treatment of the gall bladder condition may result in complete relief from all symptoms.

In view of the relative lack of emphasis upon this phase of the subject, it seems desirable to report 4 cases, 2 of cholelithiasis and 1 of perforated gastric ulcer in which the clinical findings were very strongly suggestive of coronary occlusion, and 1 of cholelithiasis and coronary disease, entirely relieved of all symptoms following cholecystectomy, possibly because coronary occlusion occurred during or soon after the operation.

Case Reports. CASE 1.—A retired merchant, aged 74 years, was examined, December 16, 1932, at the request of his home physician who had made a diagnosis of angina pectoris. This diagnosis was apparently based upon attacks of pain high in the epigastrium or beneath the lower sternum, occurring in an elderly man with arteriosclerotic changes and mild diabetes.

The first of these attacks occurred in November, 1931. There was severe pain high in the epigastrium accompanied by vomiting, lasting 3 hr., and relieved promptly by a hypodermic injection. The pain did not radiate. On the following day the patient felt quite well. There was no fever or jaundice.

A second attack occurred on November 17, 1932, ½ hr. after a heavy meal. There was very severe pain high in the epigastrium, accompanied by vomiting and lasting 2½ hr. The pain did not radiate. There was no fever or jaundice, but the patient remained in bed for 1 week. Since then he has felt weak and worn out. He has had no pain upon exertion and only slight shortness of breath.

The examination showed the patient's general condition to be remarkably good. The heart was normal in size, its rate and rhythm were normal. The heart sounds were faint, and there were no murmurs. The blood pressure was 130/80, and the brachial arteries were not thickened. The lungs were emphysematous, but there were no râles. The abdomen was negative; there was no tenderness and the liver and spleen were not enlarged. There was no edema of the extremities.

The blood count and hemoglobin were normal. The urine was normal, with the exception of a moderate amount of sugar. The electrocardiogram showed moderate left axis deviation with normal *T* waves, and was not suggestive of coronary occlusion. Roentgen ray examination showed no abnormality of the heart, but the aorta was somewhat elongated and tortuous, and its base slightly widened. Gastro-intestinal Roentgen ray studies revealed no abnormality of the stomach or duodenum. Cholecystograms after ingestion of the gall bladder dye resulted in non-visualization of the gall bladder, but also revealed a large, solitary, stratified gall stone.

The patient's symptoms were undoubtedly due to gall bladder disease. There was no evidence of heart disease. The diagnosis of angina pectoris, however, had been made and treatment for this had been instituted.

CASE 2.—A physician, aged 51, was examined, November 17, 1931. A provisional diagnosis of coronary artery disease had been made. The patient had had 7 attacks of pain in the epigastrium and precordial region. The first 5 were alike. The pain was confined to the epigastrium and was somewhat rhythmic. It bore no relation to exercise or food, excepting that all attacks occurred in the evenings of days when he felt very much exhausted. These attacks were not very severe; they lasted only 2 hr. and the patient felt quite well after the attacks. There was no nausea or jaundice.

The last 2 attacks began in the same way, but instead of relief after 2 hr., a very severe pain developed in the midprecordium, steady and not radiating, not relieved by morphin and relieved for a few minutes only by amyl nitrite. During 1 attack the blood pressure was 110 systolic, and the patient was covered with perspiration. There was no nausea, jaundice or fever. On the days following the severe attacks the patient felt quite well and was able to see his patients as usual.

The examination showed the patient to be moderately obese. The heart was normal in size; its rate and rhythm were normal. There were no murmurs. The blood pressure was 135/95. The lungs were clear. The liver and spleen were not enlarged. There was no edema.

The electrocardiogram showed slight left axis deviation, with normal *T* waves. It was not suggestive of coronary occlusion. Roentgen ray studies revealed no abnormality of the heart, lungs or stomach, but there was moderate spasm of the pylorus, the duodenal bulb was displaced somewhat posteriorly, and the gall bladder was not visualized after ingestion of the gall bladder dye. No gall stones were detected.

These findings suggested very strongly that the patient's symptoms were due to disease of the gall bladder and not of the heart.

On December 14, 1931, the patient wrote that further Roentgen ray studies had revealed spasm of the pylorus and non-visualization of the gall bladder after ingestion of the dye. He had had no further attacks.

On May 10, 1932, the home physician reported that the patient had been operated upon. The gall bladder was enlarged, its wall thickened and it contained many stones. The patient died of peritonitis following the operation.

In this case the symptoms were so strongly suggestive of coronary artery disease, particularly the transient relief from the precordial pain following the inhalation of amyl nitrite, that a provisional diagnosis of this condition was made. Further studies, however, revealed no evidence of disease of the heart, but did reveal evidence of gall bladder disease which must have been responsible for the patient's symptoms. The amyl nitrite may have relieved the pain by relaxing spasm of the pylorus or in the biliary tract.

CASE 3.—A manufacturer, aged 63, was admitted to the surgical service as an emergency at 12.30 A.M., December 10, 1930, complaining of very severe, steady pain in the midepigastrium. The pain began suddenly

3 hr. previously. It was constant, not associated with nausea or vomiting, and did not radiate. For 3 or 4 years previously he had experienced occasional cramping abdominal pains, accompanied by eructations of gas and occurring at irregular intervals after meals. He stated that his pulse had always been slow, and that he had been warned by a physician, who had examined him about 6 months previously, to restrict his activities and to avoid strenuous exertion because of elevated blood pressure and a heart condition, but he gave no history of symptoms suggesting previous heart disease.

The patient was an asthenic, elderly male who appeared acutely ill. He was ashen gray, but without apparent dyspnea or cyanosis. The oral temperature was 95° F., the pulse 52 and the respirations 16. The heart was normal in size, its rhythm regular. A definite to-and-fro pericardial friction rub was heard over the midprecordium. The heart sounds were weak. There were no signs of a valve lesion. The brachial arteries were thickened and tortuous. The blood pressure was 170/83. Throughout the upper half of the abdomen there was pronounced tenderness and muscle spasm. There was no palpable mass and the liver and spleen were not felt. The liver dullness was not obliterated, and there were no signs of ascites. The lungs were clear. There were no signs of congestive cardiac failure. The pupils and the deep tendon reflexes were normal. There was a leukocytosis of 11,650 and the urine was normal.

The surgical diagnosis was perforated peptic ulcer. The history of previous hypertension, however, the slow pulse and the obvious arteriosclerosis and, most of all, the pericardial friction sound, made it necessary to consider seriously the possibility of coronary occlusion. An electrocardiogram was taken; it showed rather flat *T* waves, much smaller than the *T* waves of an electrocardiogram taken 6 months previously, which was available for comparison. There were also occasional extrasystoles. Otherwise the curve was not abnormal, it revealed nothing definitely diagnostic of myocardial infarction. With considerable doubt regarding the diagnosis still remaining, it seemed justifiable to take the patient to the Roentgen ray room. There fluoroscopy revealed a small amount of air beneath the diaphragm, under the heart shadow, and just to the right of the gas bubble of the stomach. A film was made which confirmed this finding. The diagnosis of perforated peptic ulcer could now be made with confidence.

At operation a perforation in the anterior wall of the stomach, about 3 cm. above the pylorus, was closed and a posterior gastroenterostomy was done. Recovery was uneventful. The patient sat up on the 12th postoperative day, was soon walking and was discharged on the 20th day after operation. There were no cardiac symptoms.

Reëxamination on June 3, 1931, revealed no evidence of cardiac abnormality. The blood pressure was 140/90. In May, 1933, the patient returned to the hospital because of hematemesis. It was found that the bleeding was from a duodenal ulcer. Examination at that time again showed no evidence of cardiac abnormality. The blood pressure was 110/70 after the hemorrhage. An electrocardiogram was normal. The *T* waves were larger than those of December 10, 1930, but there were none of the changes which might suggest previous myocardial infarction.[10] The patient made a good recovery.

In this case a perforated gastric ulcer was accompanied by many findings suggestive of coronary occlusion, including a pericardial friction rub and slight, but definite changes in the *T* waves of the electrocardiogram. Rather complete studies at the time, however, gave conclusive evidence of perforated peptic ulcer, and this was confirmed at operation. Subsequent observations have ruled out coronary occlusion. The manner in which the pericardial friction rub was produced remains obscure.

CASE 4.—A factory foreman, aged 54, was first examined, November 13, 1931. He complained of vomiting, epigastric pain and shortness of breath. The vomiting began 2 years previously and gradually increased in frequency until it occurred 3 or 4 times daily. It usually occurred shortly after meals, and, as a rule, only small amounts were vomited. Slight nausea and eructation of gas often preceded the vomiting. There was no history of jaundice or abnormal stools.

The epigastric pain had likewise been present for 2 years. For a long time it occurred only upon exertion and was relieved promptly by rest, but more recently it had occurred occasionally while the patient was resting. The pain always began in the midepigastrium and radiated to the precordium, left shoulder and left arm. In the latest attacks it had also radiated to the right shoulder and right arm. During the last year shortness of breath occurred upon moderate exertion. There was no history of edema. There was a chronic, productive cough.

The patient was moderately obese. The retinal arteries showed early sclerotic changes. The lungs were somewhat emphysematous, but otherwise clear. The heart was slightly enlarged; its rate and rhythm were normal; the heart sounds were distant and there were no murmurs. The brachial and radial arteries were not thickened. The blood pressure was 120/80. There was slight tenderness in the right upper quadrant of the abdomen, but the liver was not enlarged and there were no abdominal masses. There was no jaundice and no edema. There was a stricture of the urethra.

The Kahn reaction of the blood was negative. The urine and stool were normal. The gastric analysis was normal. Roentgen ray examination of the upper gastro-intestinal tract was negative. Fluoroscopically the heart appeared broad and the base of the aorta slightly widened.

The patient was given small doses of digitalis and metaphyllin. He could not take the latter because of gastric symptoms; he also stated that he could not take nitrites because they produced headache.

Because he failed to improve he entered the hospital on December 12, 1931. The examination was as before. The urine, stool, blood and spinal fluid were normal. Cholecystograms after the oral administration of the gall bladder dye revealed faint visualization of the gall bladder with evidence of a single, large gall stone. Roentgen ray examination showed slight, generalized enlargement of the heart and broadening of the base of the aorta. An electrocardiogram, taken on December 14, 1931, was normal, with the exception of slight depression of the *T* waves attributed to digitalis. While at rest in the hospital the patient had several attacks of epigastric pain which radiated not only to both arms, but also to both legs. Some of these attacks were relieved by nitroglycerin. Amyl nitrite was tried frequently without success. The diagnoses of angina pectoris, cholecystitis and cholithiasis were made.

On December 29, 1931, a cholecystectomy was performed under avertin, nitrous oxid and ether anesthesia. There was chronic inflammation of the gall bladder wall and one large calculus. During the operation the blood pressure fell to 68/50, but within a few hours it rose to normal and remained normal thereafter. For several days after the operation the patient complained at times of pain in the abdomen and chest, but this was regarded as the usual postoperative discomfort. His general condition was good at all times, and he was allowed up on the 14th day after operation. On January 18, 1932, the 20th day after operation, a second electrocardiogram was taken. It showed changes in the *Q–R–S* and *T* deflections which were characteristic of recent coronary occlusion. The patient continued to be up and about, without any pain, vomiting or shortness of breath. Electrocardiograms taken on January 25 and 29 were similar to the curve of January 18. He left the hospital on January 29.

The patient returned, as advised, for a check-up examination on March 16, 1932. He had been entirely free from symptoms referable to his heart or gastro-intestinal tract, and examination revealed no significant abnormality of the heart. The blood pressure was 115/75. An electrocardiogram on this date, however, was quite similar to the curves of January 18, 25 and 29, 1932.

This patient had gaseous eructations, nausea and vomiting which were attributed to gall bladder disease. In addition he had epigastric pain, radiating to the shoulders and arms, and shortness of breath, both definitely related to exertion and attributed to coronary disease. Following cholecystectomy he was completely relieved of the cardiac as well as the gall bladder symptoms. While under observation he must have experienced occlusion of a small branch of a coronary artery producing a relatively small myocardial infarct. It is possible that the pain of effort was due entirely to narrowing of the coronary branch which finally became occluded, so that after the occlusion the pain no longer occurred.

Summary. It has been pointed out repeatedly that in coronary occlusion an erroneous diagnosis of upper abdominal disease may be made. But little attention has been given to the fact that in upper abdominal disease a mistaken diagnosis of coronary disease is sometimes made. In view of the popularity now enjoyed by the diagnosis of coronary occlusion, and the facility with which it is made, sometimes upon inadequate evidence, it seems desirable to emphasize the fact that upper abdominal disease may simulate coronary disease to a very striking degree.

Four illustrative cases are presented. In the first two the symptoms were caused by gall bladder disease, but erroneous diagnoses of coronary disease had been made. The third case was one in which perforation of a gastric ulcer was accompanied by many of the manifestations of acute coronary occlusion, and only rather complete studies revealed the true condition. In the fourth case both cholelithiasis and coronary disease were present, and the patient was entirely relieved of all symptoms following cholecystectomy, possibly because coronary occlusion occurred during or soon after the operation. Unless the symptoms and signs are unequivocal, the diagnosis of angina pectoris or coronary occlusion should not be made until upper abdominal disease has been excluded.

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THE INITIAL VENTRICULAR DEFLECTION OF THE ELECTROCARDIOGRAM IN CORONARY DISEASE.

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Recent years have been productive of a large and varied literature dealing with the electrocardiographic diagnosis of coronary disease and coronary occlusion. A large part of the work done has had as its main object the evaluation of changes in the form of the *R–S–T* segment and *T* wave. There is no doubt that characteristic changes in the shape of these ventricular deflections are of great value in the diagnosis of recent coronary occlusion, but it is well known that they are more or less transitory.

A possible relationship between abnormalities of the initial ventricular deflections and coronary disease was first suggested by Pardee[1] who pointed out that large *Q* waves in Lead III occur very frequently in association with the anginal syndrome. As a result of his studies he came to the conclusion that the presence of a *Q* wave in Lead III had diagnostic value when this deflection is followed by an upward excursion (*R*) but no *S* wave, and is at least $\frac{1}{4}$ as large as the largest *Q–R–S* deflection in any lead. Pardee attached no significance to large *Q* waves in Lead III when definite right axis deviation was present or when the initial deflections in Lead III resembled the letter *M* or the letter *W* in shape. In a group of curves meeting these qualifications he found 63 per cent to be associated with the anginal syndrome.

The diagnostic criteria established by Pardee have been subjected to considerable scrutiny by other investigators. The frequency of the anginal syndrome in different groups of cases satisfying the requirements stated has been reported by various observers as follows: Ziskin[2] 14%, Strauss and Feldman[3] 16%, Edeiken and Wolferth[4] 16%, Willius[5] 38.3%, Ashman *et al.*[6] 42%, Pardee[1] 63%. An analysis of the data given by these workers indicates that the electrocardiographic signs enumerated are more frequently associated with hypertension uncomplicated by angina pectoris or coronary occlusion, than with the anginal syndrome. Several investigators have pointed out that a transverse position of the heart may play an important part in the production of large *Q* deflections in Lead III.

It is evident that if the changes in the initial ventricular deflections produced by coronary disease are to become of any great diagnostic value they must be defined in a more satisfactory manner. The advantages that may be gained from the more certain differentiation of these changes from similar changes due to other causes

will be appreciated when it is realized that, unlike the characteristic but more or less temporary changes in the final ventricular deflections, they are permanent.

Recently, Wilson[7] and his coworkers have emphasized the diagnostic value of the *Q–R–S* changes and their lasting character. They showed that two distinct types of abnormal *Q–R–S* deflections are frequently encountered in cases of coronary occlusion. The first of these is illustrated by the curves shown in Fig. 1 (*A* and *B*). Attention was drawn to the following distinctive features of this type of electrocardiogram: (1) the conspicuous and, in most instances, rather broad *Q* wave in Lead I; (2) the small amplitude of the *R* deflection in Lead I; (3) the absence of a *Q* wave in Leads II and III; and (4) the frequent presence of a large *S* wave in Leads II and III.

The second type of curve emphasized for its diagnostic value in coronary occlusion is illustrated by the tracings shown in Fig. 1 (*C* and *D*). Here the important characteristics pointed out were: (1) a conspicuous *Q* wave in Leads II and III, (2) the absence of *Q* in Lead I, and (3) the relatively small amplitude of the initial deflections in Lead II (Fig. 1, *D*).

These two types of abnormal initial deflections were referred to as curves of the *Q*1 and *Q*3 type, respectively; the former was found to be associated in most cases with infarcts involving the anterior, and the latter with infarcts involving the posterior wall of the heart.

One of the main purposes of the present study was to ascertain how frequently curves of the *Q*1 and *Q*3 types are encountered in cases in which there is no other reason for suspecting coronary disease. The second purpose was to determine what criteria, if any, could be used to differentiate between the *Q–R–S* changes due to coronary disease and similar changes due to other causes. The material utilized was obtained from the electrocardiographic files of the Heart Station of the University Hospital. Over 19,000 curves have been taken in this Station since 1923. Approximately 7000 are available for study in printed form; the remainder were not definitely abnormal and were not printed. All the printed curves were examined and those which showed abnormal *Q–R–S* deflections of the kinds in question were carefully studied. The corresponding case records were then analyzed, and various criteria were tested as to their value in the electrocardiographic diagnosis of coronary disease.

Electrocardiograms of the Q3 Type. The first studies dealt with curves of the *Q*3 type which conformed to the standards set up by Pardee, and, in addition, displayed in Lead II a *Q* wave at least 1 mm. in amplitude. It was soon found that it would be advisable to omit one of Pardee's requirements; namely, that *Q*3 be followed by a summit (*R*) but no *S* deflection. The basis for this omission was the discovery that a number of cases of definite coronary occlu-

sion with large Q waves in Lead III failed to conform to this standard. Fig. 1, *D*, the electrocardiogram from a case of coronary occlusion proved by autopsy, illustrates this point. For similar

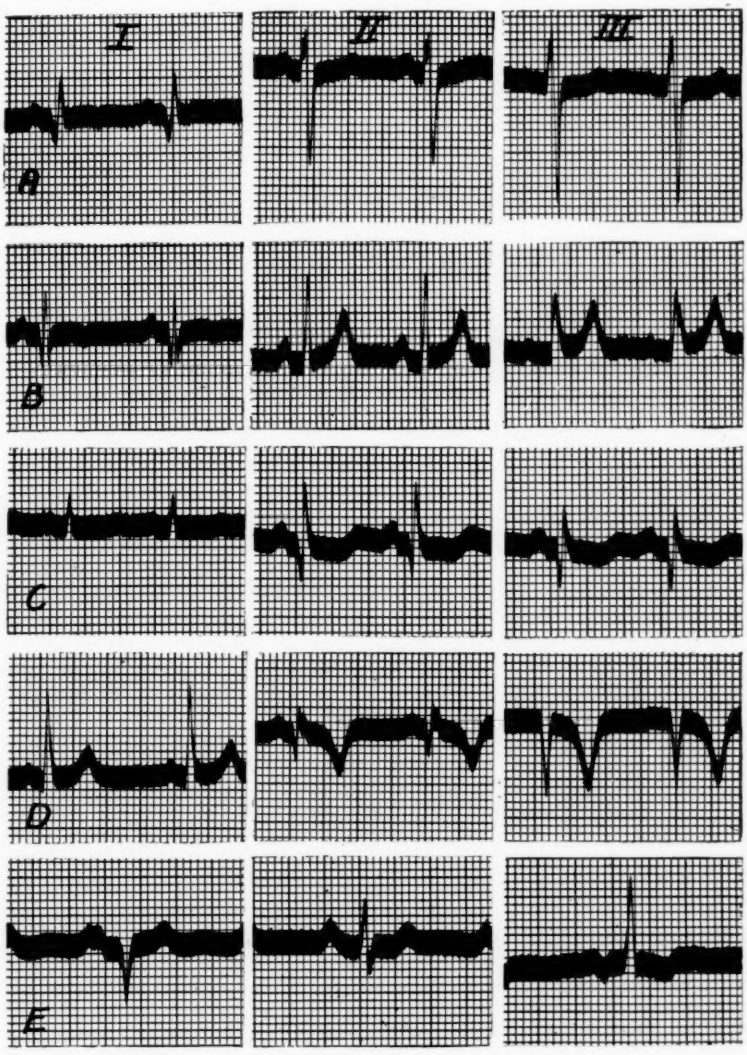

FIG. 1.—*A* and *B*, curves of the $Q1$ type; *C* and *D*, curves of the $Q3$ type; *E*, an electrocardiogram showing large Q-waves in Lead I. This curve is from a case of mitral stenosis.

reasons it was found unnecessary to eliminate curves with slight notching of the downstroke of $Q3$ (the W complex of Pardee). Curves showing right axis deviation were excluded.

The number of electrocardiograms which met these qualifications was 96. A study of the case records revealed 31 examples of coronary occlusion and 29 cases of angina pectoris (Table 1, A). The remaining patients gave no history and showed no physical signs suggesting anginal pain or coronary occlusion.

TABLE 1.—*Q3* GROUP.

	Criteria.	Total cases.	Coronary disease.			No evident coronary disease.	Percentage coronary disease.
			Coronary occlusion.	Angina pectoris.	Total.		
A	*Q3* at least 25% of largest *Q–R–S* deflection *Q2* at least 1 mm. Left axis deviation or normal axis	96	31	29	60	36	62.5
B	*Q3* at least 50% of largest *Q–R–S* deflection *Q2* at least 25% of *R2* Left axis deviation or normal axis	44	25	11	36	8	81.8
C	Same as under B, and in addition *T*-wave inversion in Leads II and III, but not in Lead I	22	18	4	22	0	100.0

It was felt that more satisfactory results might be obtained by further modifications of the criteria used. The requirements finally selected were as follows: (1) an initial downward deflection in Lead III having an amplitude at least $\frac{1}{2}$ as great as the largest *Q–R–S* deflection in any lead, (2) an initial downward deflection in Lead II at least $\frac{1}{4}$ as large as *R2*, and (3) left axis deviation or a normal electrical axis. Clear evidence of angina pectoris or coronary occlusion was obtained in 81.8% of the 44 cases which conformed to these standards (Table 1, B). Of the 8 patients without evident coronary disease, 4 had generalized arteriosclerosis and 1 arteriosclerotic heart disease. It is possible that these patients had coronary disease which was not recognized or could not be recognized clinically. The other 3 patients with no evident coronary disease included 2 with adenomatous goiter, 1 of whom showed definite hyperthyroidism. The 3d suffered from obesity and cholecystitis, but had no demonstrable cardiac disease.

When *T* wave inversion in Leads II and III without inversion in Lead I was added to the requirements enumerated above, the number of cases was reduced to 22, all of which were clear examples of coronary disease (Table 1, C). It is therefore felt that when both *Q–R–S* changes and *T* wave changes of the type under consideration are found the presence of coronary disease is practically certain. In the absence of changes in the final deflections, however, a fairly

high degree of diagnostic accuracy is obtained from the Q–R–S variations alone.

Electrocardiograms of the Q1 Type. Curves of the $Q1$ group were analyzed in a similar manner. The results are summarized in Table 2. The first step was to remove from the files all curves

TABLE 2.—$Q1$ GROUP.

	Criteria.	Total cases.	Coronary disease.			No evident coronary disease.	Percentage coronary disease.
			Coronary occlusion.	Angina pectoris.	Total.		
A	$Q1$ at least 1 mm $R1$ less than 5 mm. $Q1$ at least 20% of largest R	32	13	4	17	15	53.1
B	Same as under A, and in addition curves eliminated in which no $R1$ is present	23	13	4	17	6	73.9
C	Same as under B and, in addition, inversion of $T1$, without inversion of $T2$ or $T3$	14	10	3	13	1	92.8

which showed the following characteristics: a Q wave in Lead I measuring at least 1 mm. and at least $\frac{1}{5}$ as large as the largest R in any lead, and an $R1$ not exceeding 5 mm. in height. The incidence of coronary disease in this group of cases (Table 2, A) was relatively low because of the inclusion of a number of cases of mitral stenosis. Most of these and a few others in which there was no evident coronary disease were eliminated when all curves that failed to show a summit (R) following $Q1$ were excluded. A curve from a case of mitral stenosis, thus eliminated, is shown in Fig. 1, E. The 6 cases without evident coronary disease that were not eliminated were classified as follows: mitral stenosis 2, congenital heart disease 1, arteriosclerotic heart disease with congestive failure 2, exophthalmic goiter 1. It was not found feasible in these studies to use in any way the size of the S wave in Leads II and III in developing diagnostic criteria, although it was found that a majority of the cases of coronary disease displayed large waves of this type.

The addition of changes in the final ventricular deflection of the $T1$ type raised the incidence of coronary disease to 92.8% (Table 2, C). One case of congenital heart disease showed both Q–R–S and T wave changes and could not be excluded.

It is evident that the diagnostic value of electrocardiographic changes of the $Q1$ type is considerably enhanced by the fact that those cases most often causing confusion (mitral stenosis and congenital heart disease) are as a rule readily eliminated by the clinical

findings. If the 2 cases of mitral stenosis and 1 case of congenital heart disease are left out of consideration the incidence of coronary disease under 2 B becomes 85%, a figure comparable to that obtained for curves of the *Q*3 type.

Incidence in Coronary Occlusion. It seemed advisable to determine the frequency of curves fulfilling the requirements described in a group of cases in which there was a definite history of coronary occlusion. Seventy-four cases were collected in which a certain diagnosis of coronary occlusion could be made from the history, from the precordial electrocardiogram, or from autopsy findings. Thirteen of these satisfied the criteria given in Table 2, B. Twenty-five curves were of the *Q*3 type and met the requirements given in Table 1, B. Thus 38 cases (51.3% of the total number) showed initial ventricular deflections of either the *Q*1 or the *Q*3 type, as defined in this article.

Initial ventricular variations of the kinds described are, therefore, infrequent in conditions other than coronary disease, but occur in approximately $\frac{1}{2}$ of the cases of coronary thrombosis. It is, of course, obvious that any modification of the diagnostic criteria which tends to eliminate non-coronary cases also excludes some cases of coronary disease.

Summary. Two types of *Q–R–S* deflections are characteristic of coronary disease; the *Q*1 type and the *Q*3 type. Curves of the *Q*1 type may be defined as those in which *Q*1 measures at least 1 mm. and is at least $\frac{1}{3}$ as large as the largest *R* deflection in any lead, and in which there is a definite *R* wave in Lead I, measuring less than 5 mm. in amplitude. Curves of the *Q*3 type may be defined as those in which *Q*3 is at least $\frac{1}{2}$ as large as the largest *Q–R–S* deflection in any lead, and in which *Q*2 is at least $\frac{1}{4}$ as large as *R*2. Curves showing right axis deviation must be eliminated.

The relatively permanent nature of these changes in the *Q–R–S* deflections in contrast to the more or less transitory changes in the *R–S–T* segment and in *T* greatly enhances their value in the recognition of coronary disease, and particularly in the diagnosis of old myocardial infarcts.

Indebtedness is acknowledged to Dr. Frank N. Wilson for the suggestions and help rendered by him in the carrying out of this study.

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ATYPICAL BUNDLE-BRANCH BLOCK WITH A FAVORABLE PROGNOSIS.

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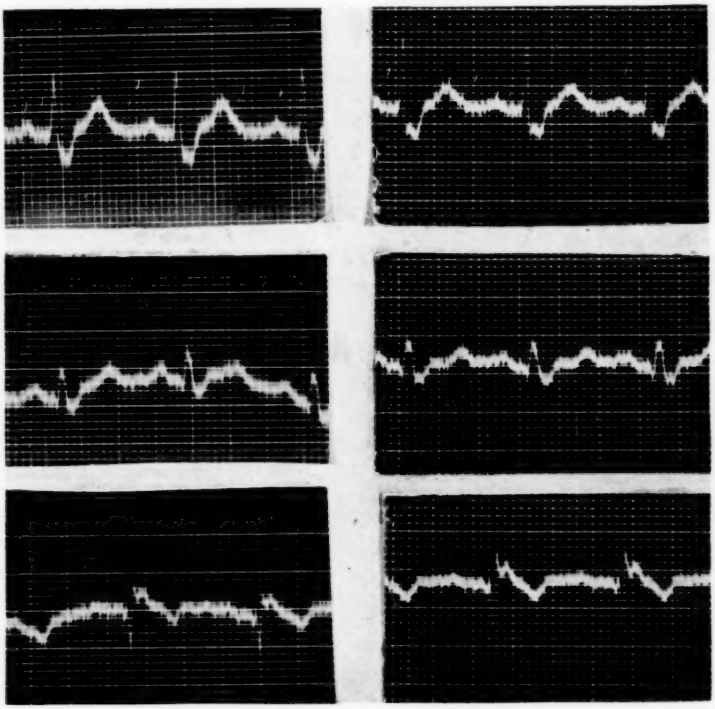
The following cases illustrating a type of atypical bundle-branch block are reported because of the longevity of 2 patients and the mildness of the cardiac symptoms in all of them.



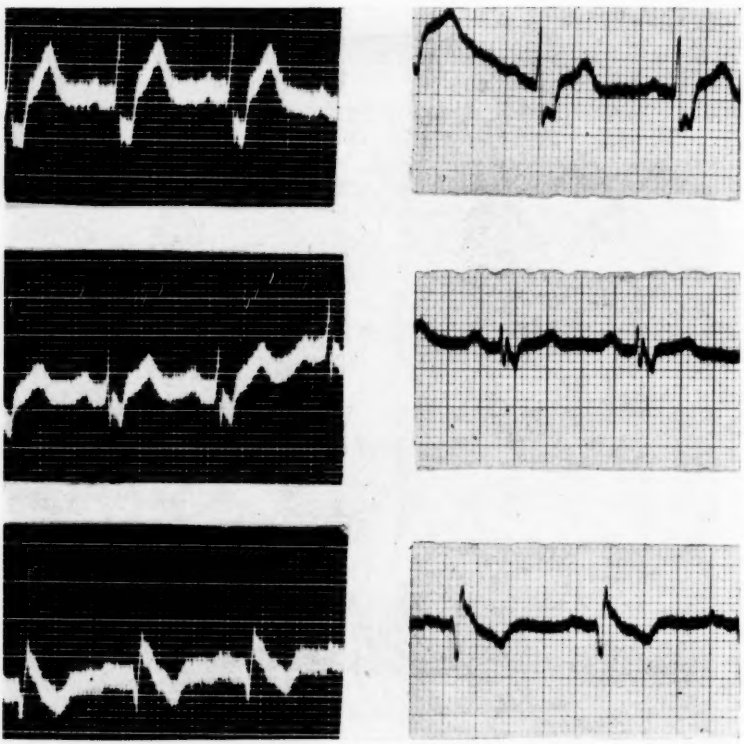
April, 1923. September, 1930.

Fig. 1.—Case 1. Other electrocardiograms taken in the interval between the above dates show the same configuration.

Bundle-branch block generally indicates serious myocardial damage. The literature and textbooks have called attention to the poor cardiac reserve and early mortality of patients having bundle-

branch block. Graybiel and Sprague have analyzed 395 cases of bundle-branch block. Their follow-up of 308 cases showed an average duration of life of 1 year and 2 months in 223 fatal cases. The chief cause of death was cardiac failure. Eighty-five patients who are living for an average of 2 years and 11 months have a limited cardiac reserve.

The electrocardiographic records in all of the cases here reported of atypical bundle-branch block, except for minor variations, are



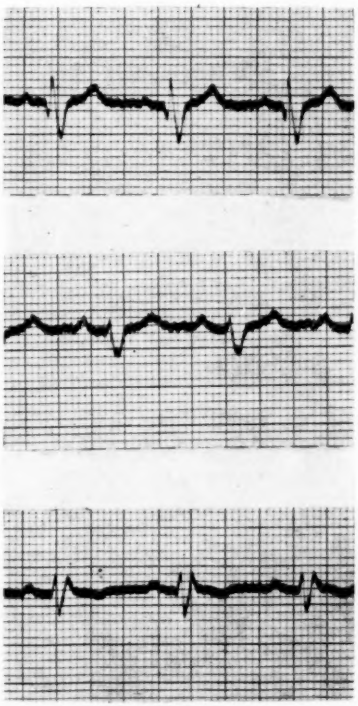
1925. 1932.

FIG. 2.—Case 2. Other electrocardiograms taken in the interval between the above dates show the same configuration.

similar. A brief description of the curves is as follows: 1, *Q–R–S* complex has a prolonged duration; 2, Lead 1, an *R* wave of moderate amplitude and short duration is followed by a prolonged notched *S* wave. The latter has a smaller amplitude than the *R* wave. 3, the *T* wave is upright in Leads 1 and 2; 4, the initial phase of the *Q–R–S* complex in Lead 3 is downward, returning quickly to above the isoelectric line where the curve is notched and prolonged. The *T* wave in Lead 3 is directed downward; 5, except for the lower

amplitude the Q–R–S complex in Lead 2 is similar in most curves to Lead 1. The character of the curves is confusing in regard to the localization of the lesion in the conducting system and is referred to as atypical bundle-branch block.

All of our cases of atypical bundle-branch block have occurred in males. One patient is living $11\frac{1}{2}$ years after the diagnosis was made; 1, 8 years after; 1 seen $2\frac{1}{2}$ years ago with this type of block



May, 1931.

FIG. 3.—Case 3. Other electrocardiograms taken since this date show the same type of curve.

is doing hard work; 1 recently observed in a hospital, a man aged 70, exhibiting this type of block left the institution and has not been subsequently heard from; 1 first examined $1\frac{1}{2}$ years ago has continued his occupation.

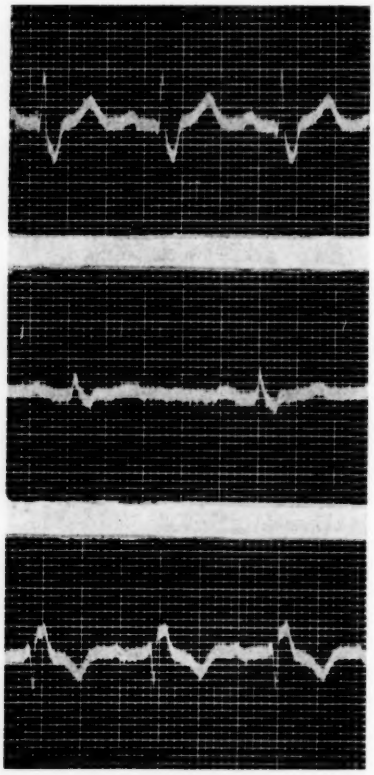
Synopsis of Case Histories. CASE 1 (Fig. 1).—H. S., aged 72, $11\frac{1}{2}$ years ago was referred to one of us on account of the symptoms of acute indigestion and slight dyspnea. His occupation necessitated much stair climbing. He discontinued this occupation and is in fairly good health at the present time. Numerous electrocardiograms, taken during this period, show the same type of curves.

CASE 2 (Fig. 2).—T. B., physician, aged 54, actively engaged in the practice of medicine; hypertensive individual. Eight years ago, on account of numerous extrasystoles, decided to have an electrocardiogram taken. Until

the present time frequent electrocardiograms show the same curves. He has not curtailed his activities.

CASE 3 (Fig. 3).—A. B., male, aged 51, was first seen in May, 1931, complaining of moderate pain in the left precordial region. He does hard physical work and has not changed his occupation since his first visit, and the electrocardiogram remains the same.

CASE 4 (Fig. 4).—B. C., aged 78, was admitted to the hospital on account of vertigo. A routine electrocardiogram showed the same type of atypical bundle-branch block curve. He had no cardiac symptoms.



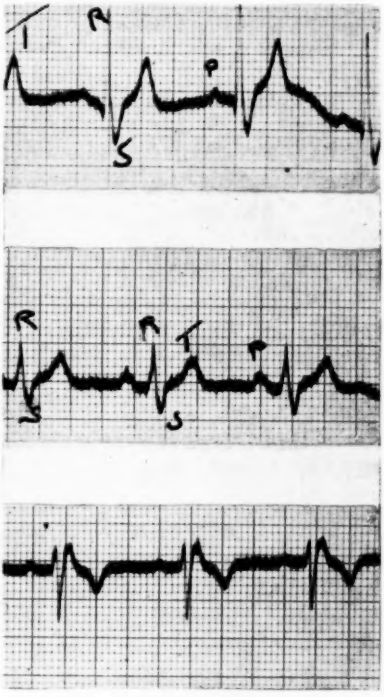
January, 1929.

FIG. 4.—Case 4. No other electrocardiogram taken on this case.

CASE 5 (Fig. 5).—M. S., aged 49, insurance collector, was referred to one of us on account of vertigo and vague epigastric distress with the request that an electrocardiogram be taken. It showed the same type of atypical bundle-branch block curve. He was very much distressed on account of the prognosis given him, based on an electrocardiogram taken previously and interpreted as one of hopeless invalidism. He continued his occupation after reassurance. A recent electrocardiogram shows the same type of atypical bundle-branch block.

Comment. Since the more frequent use of the electrocardiograph and the tendency to base prognosis on instrumental rather than on

clinical findings, misinterpretation of the graphic records of this type of atypical bundle-branch block may cause great apprehension, chronic invalidism and impairment of earning power.



May, 1932.

FIG. 5.—Case 5. Other electrocardiograms taken since this date show the same type of curve.

Summary. 1. Five cases of atypical bundle-branch block showing similar curves are presented.

2. One of these patients is alive at the end of 11½ years, at the age of 72. Another is alive at the end of 8½ years, at the age of 54.

3. Four have no cardiac symptoms at the present time; one we have not been able to follow.

4. Numerous electrocardiograms in 4 of these patients have remained the same through many years.

5. Hypertension is present in only 1 of these patients.

NOTE:—The Editor would like to mention in this connection another example of a healthy man (T. C. H.) aged 47 who repeatedly for the last 16 years has shown a so-called bundle-branch block without any evidence of cardiac disease or diminution of cardiac reserve. The possibility of an anomalous course of the distribution of the healthy branches and terminals of His' bundle should be considered in such cases.

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THE FREQUENCY AND SIGNIFICANCE OF RIGHT BUNDLE-BRANCH BLOCK.*

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For many years it has been the universal opinion that myocardial disease interrupts one branch of the His bundle very much more often than the other. This opinion is based upon the relative frequency of the 2 types of electrocardiograms currently attributed to bundle-branch block. According to different observers, the common type right branch block of the older terminology is seen 5 to 10 times as often as the less common. It is evident that our ideas respecting the incidence of bundle-branch lesions of both kinds depend upon the criteria generally accepted for the classification of electrocardiograms with broad *Q–R–S* deflections. Observations made in this laboratory suggest that both varieties of branch block are considerably more common than is at present supposed.

It has been shown[1] that precordial leads taken by pairing an exploring electrode placed over the precordium with an indifferent electrode placed on the left leg, or with a central terminal connected through equal and sufficiently large resistances to the 3 extremity electrodes, are of great value in locating the conduction defect in intraventricular and particularly in bundle-branch block. These precordial leads are so taken that relative negativity of the exploring electrode produces an upward deflection. The majority of precordial electrocardiograms show a sudden and pronounced upward excursion at some time during the *Q–R–S* interval. This *chief upstroke* represents a sudden large negative variation in the potential of the exploring electrode, and signals the arrival of the excitation process at the epicardial surface of the subjacent portions of the ventricular wall. In bundle-branch block the upstroke is early when the exploring electrode is placed over the contralateral and late when it is placed over the homolateral ventricle. The time of the chief upstroke is measured with reference to the first ventricular deflection in Lead I, which is taken simultaneously with each precordial lead.

In cases in which the standard electrocardiograms exhibit all the features regarded as characteristic of bundle-branch block of the less common variety, the chief upstroke is early in leads from the left side and late in leads from the right side of the precordium. Precordial curves with similar time characteristics have, however,

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been obtained in all patients tested who had standard electrocardiograms in which the ventricular complex showed a *Q–R–S* interval of 0.12 sec. or more and a broad *S* deflection in Lead I. It has, therefore, been suggested that all such electrocardiograms represent complete right bundle-branch block.[2]

It is the purpose of this article to present the results of an analysis of all the electrocardiograms of the kind mentioned that could be found in the files of this laboratory,* and of the case histories of the patients from whom these curves were obtained. The chief object of the study was to determine the relative frequency of right and left branch block and with what kinds of heart disease they are most often associated. It was thought that such a study might indicate the nature of the factors that determine which of the several forms, presently to be described, the ventricular complex will take when right bundle-branch block develops.

As a first step, all the electrocardiograms which showed a *Q–R–S* interval of 0.12 sec. or more were critically examined; 70 curves were found which were regarded as representing complete right bundle-branch block. In addition to a lengthened *Q–R–S* interval, all these curves showed a broad *S* deflection in Lead I. None were included in which the value of the chief initial deflection failed to exceed 5 mm. in at least 1 lead.

The curves selected fell naturally into 4 more or less distinct groups:

GROUP 1.—The 14 curves in this group showed all the features generally accepted as necessary for the interpretation of bundle-branch block of the less common type (Fig. 1, *A*, *B*, *C*). In Lead I the chief initial deflection of these curves is a broad downward excursion, *S*, which is preceded by a smaller upward movement, *R*. T_1 is upright. In Lead III, the chief initial deflection is a broad, notched, upward excursion, *R*, which is preceded by smaller dip, *Q*. T_3 is inverted.

GROUP 2.—Twenty-three curves were similar to those of the preceding group in all respects except that in Lead I the amplitude of the *R* spike was greater than that of the *S* deflection. (Fig. 1, *D*.)

GROUP 3.—In this group, 28 curves were placed because of the character of the initial deflection in Lead III. In these curves the most conspicuous *Q–R–S* deflection in this lead is a slender, deep, inverted spike, usually preceded by a small and invariably followed by a broad summit (Fig. 2, *A*, *B*). The amplitude of this last deflection is less than that of the inverted spike. In Lead I the ventricular complexes are similar in all respects to those of the curves placed in Group 2.

GROUP 4.—Only 5 curves were placed in this group. They were separated from those of the preceding groups chiefly because they lacked a broad upward movement in Lead III. In this lead the

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initial deflection is a small summit, which is followed as in Group 3 by a deep inverted spike (Fig. 2, *C*, *D*). At its apex the inverted spike is narrow, but the ascending limb, after rising sharply, usually shows a pronounced notch, beyond which its ascent is gradual (Fig. 2, *D*). The base of the inverted spike is, therefore, greatly broadened. In some instances this broad upward movement in

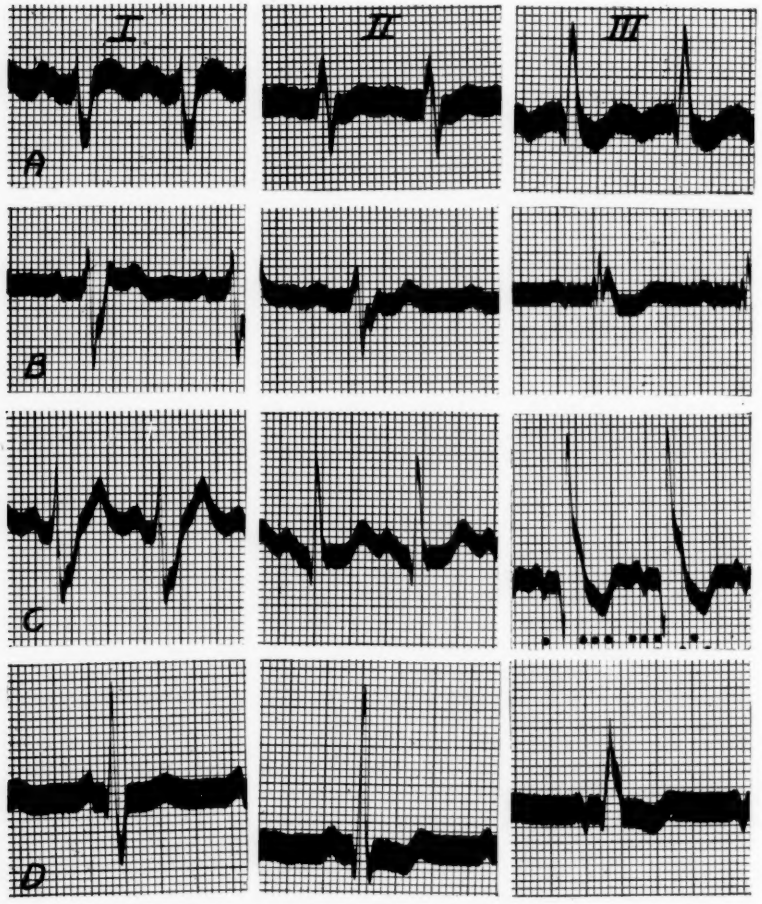

FIG. 1.—*A*, *B*, and *C*, electrocardiograms of the type placed in Group 1. *D*, an electrocardiogram of the type placed in Group 2.

Lead III is absent, and the ascending limb returns quickly to the baseline and does not leave it during the remainder of the *Q–R–S* interval (Fig. 2, *C*). The distinguishing feature of these curves is the absence of a broad upstroke at the end of the *Q–R–S* interval in Lead III. In Lead I the *Q–R–S* deflections are similar to those which characterize Groups 2 and 3, except that *R* is usually taller

and broader and S less conspicuous. T_3 is usually upright. Some of the curves of the last 2 groups (3 and 4) might easily be confused with those that represent left bundle-branch block, from which they may be differentiated by the presence of a conspicuous and broad S in Lead I.

An analysis of the case records of the patients from whom these 70 curves were obtained, showed that no single etiologic factor or

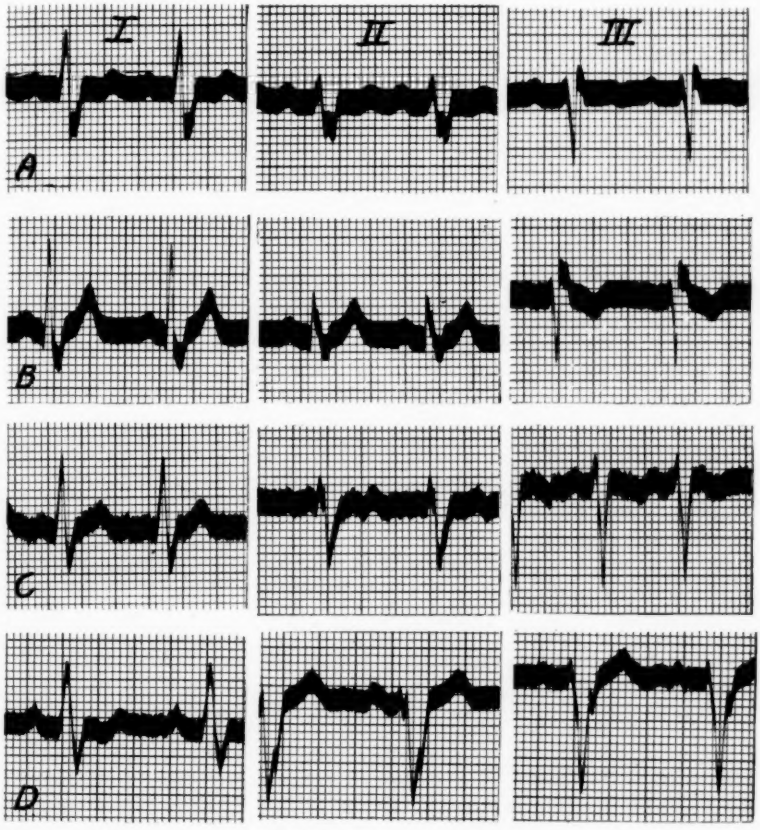

FIG. 2.—A and B, electrocardiograms of the type placed in Group 3. C and D, electrocardiograms of the type placed in Group 4.

kind of heart disease was responsible for the whole of any one of the 4 groups. It was anticipated that patients with rheumatic heart disease and mitral stenosis uncomplicated by aortic insufficiency, and, therefore, with right or at least with no left ventricular preponderance, would, on developing right bundle-branch block, display curves of the kind placed in Group 1 or 2. In 5 of these cases with these specifications, the curves were of the anticipated varie-

ties. In 1 case of congenital heart disease the electrocardiogram was of the type placed in Group 2.

It was also thought that patients with right branch block and vascular hypertension of sufficient duration to have produced left ventricular preponderance would be more likely to display curves of the varieties placed in Groups 3 and 4. Only 3 of the 11 cases of this kind showed curves of the type anticipated; in the remaining 8, the curves belonged to Group 1 or 2.

The majority of 46 patients with arteriosclerotic heart disease displayed curves belonging to Group 1 or 2. Curves of this kind were also recorded in 1 case of primary nephritis and secondary hypertension, in 2 cases of syphilitic heart disease with aortic insufficiency and in 2 cases of thyroid heart disease.

These observations do not suggest that the left axis deviation displayed by the curves placed in Groups 3 and 4 is due to preponderant hypertrophy of the left ventricle. Preponderant hypertrophy of the right ventricle would not be expected to influence the initial portion of the *Q–R–S* complex in complete *right* bundle-branch block since the excitation of the right ventricle in this condition is a relatively late event, and the first part of the curve is, therefore, written by the left ventricle. It is believed that the position of the heart, infarction of the septum or free wall of the left ventricle, and preponderance of the left ventricle are the chief factors whose absence or presence, singly or in combination, accounts for the variations of the form of the initial deflections of the *Q–R–S* complex observed in right branch block.

The third purpose of this study was to gain some conception of the relative incidence of right and left bundle-branch block and find out in what kinds of heart disease these conditions most often occurred.

There were 103 curves which showed the characteristic changes of complete left bundle-branch block. All had the *Q–R–S* interval increased to 0.12 sec. or more, and the amplitude of the chief initial deflection exceeded 5 mm. in at least 1 of the 3 standard leads. Since the examination of the same material disclosed only 70 cases of complete right bundle-branch block, complete left bundle-branch block appears to be the more common in the ratio of 103 to 70.

Of the 103 patients with left branch block, 86 had records that were available for the more detailed analysis that follows. Reference to Table 1 will show that 70% of all patients with branch block of either type had arteriosclerotic heart disease. The average age of these 110 patients with arteriosclerotic heart disease at the time the conduction defect was discovered was 64 years. The vast majority were men. The heart was of normal size in at least $\frac{1}{3}$ of the cases, and on the routine physical examinations there were no objective signs of congestive heart failure in at least $\frac{2}{3}$. Many of the patients presented little or no clinical evidence of cardiovascular

disease on routine physical examination. Further reference to the table will show that lesions of the left bundle branch are more common than lesions of the right, both in arteriosclerotic and in hypertensive heart disease. The patients with hypertensive heart disease, however, almost all showed evidence of cardiovascular disease on routine physical examination and almost ½ of them were women. The average age in the hypertensive group was 54 years. The single patient with rheumatic heart disease and left bundle-branch block had mitral stenosis with aortic insufficiency, while the 7 patients with the same kind of heart disease and right bundle-branch block had only mitral stenosis. These findings would suggest that the conduction defect is more likely to occur in the ventricle which is subjected to the greater strain.

TABLE 1.—THE RELATIVE FREQUENCY OF RIGHT AND LEFT BUNDLE-BRANCH BLOCK IN VARIOUS TYPES OF HEART DISEASE.

Etiology.	Left branch block.	Right branch block.	Per cent.
Arteriosclerotic heart disease	64	46	70.0
Hypertensive heart disease	15	11	17.8
Rheumatic heart disease	1	7	4.9
Syphilitic heart disease	4	2	3.6
Thyroid	2	2	2.5
Chronic nephritis with hypertension	..	1	0.6
Congenital heart disease	..	1	0.6
Total	86	70	100.0

The incidence of physical signs usually described as suggestive of a complete bundle-branch lesion was also noted in the 156 case records examined; the presence of a visible or palpable double apical systolic thrust was recorded only once; reduplication of the 1st or of the 2d heart sound was recorded 8 times; gallop rhythm, 13 times; there was no instance in which asynchronous systolic murmurs were detected. The presence of a bundle-branch lesion was suspected in only 1 instance before the electrocardiogram had been taken. Of the patients, 24% gave no symptoms and presented no signs of heart failure; 21% had no cardiac enlargement; and 60% had no physical signs of congestive heart failure. On the other hand, only 9% had marked cardiac enlargement. These findings indicate that the average patient with bundle-branch block shows little evidence of cardiovascular disease on routine physical examination, and one is frequently surprised when the electrocardiogram discloses a serious conduction defect. Unless an electrocardiographic examination is made more or less routinely in patients above the age of 40 years, many bundle-branch lesions may escape detection.

Conclusion. In the files of this laboratory curves of the variety ascribed to complete interruption of the left branch of the His bundle are somewhat more common than those interpreted as evi-

dence of interruption of the right branch (newer terminology). The proportion is 103 to 70. Right bundle-branch block is far more common than hitherto supposed. Seventy curves of the right bundle-branch type fell naturally into 4 more or less distinct groups, differentiated one from another by the character of the *Q–R–S* deflections. Only a small percentage of the patients with complete right bundle-branch block displayed diphasic ventricular complexes of the less common variety. The position of the heart, infarction of the interventricular septum or free wall of the left ventricle and preponderance of the left ventricle are probably the chief factors, whose absence or presence, singly or in combination, accounts for the variation in the form of the initial deflections encountered in curves from patients with complete right bundle-branch block. Both right and left branch block are considerably more common in arteriosclerotic heart disease than in the other etiologic types. There is often little or no evidence of cardiovascular disease on routine physical examination. When patients with rheumatic heart disease and mitral stenosis develop bundle-branch block, the conduction defect is almost invariably on the right side. In the case records examined, only 1 instance was encountered in which the routine physical examination suggested bundle-branch block.

Thanks are given to Dr. Frank N. Wilson for his constant guidance and suggestions during the course of this study.

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PERSISTENT FUNCTIONAL ALBUMINURIA.

ANALYSIS OF 58 CASES WITH RESULTS OF THYROID AND CALCIUM MEDICATION.

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THERE is at present no satisfactory explanation for so-called functional albuminuria. Physicians engaged in the medical care of adolescents are frequently confronted with this form of urinary disturbance and are often at a loss to know the proper disposition of the patient. While the abnormality does not appear to be harmful, the question of treatment, especially restriction of activities, frequently arises. Aside from this we are, of course, interested in the etiology of functional albuminuria and, if possible, removal of the cause. The patient is not so easily disposed of as Fishberg[1] would have us believe, by simply establishing a diagnosis and then

dismissing him by saying no treatment is indicated. To many physicians, especially those engaged in general practice, the finding of albumin in the urine means kidney disease, calling for removal of foci of infection, restriction of physical activities, lessened exposure, dieting in the form of protein restriction and iron medication. Every year we receive several letters from family physicians requesting that boys be excused from all forms of exercise because of the finding of albumin in their urine. In some instances even a fall in the scholastic standing of the student has been attributed to albuminuria, which supposedly affected his health.

Functional albuminuria was described as early as 1886 by Pavy,[2] who suggested poor posture as the cause of this abnormality. Since that time many other theories have been advanced to explain functional albuminuria and various names have been applied to the abnormality, the most recent being "benign albuminuria" (Fishberg).[1] Until we have definite proof of the cause and significance of these unexplained albuminurias, it would be better to call them idiopathic or essential albuminurias. It is probably true that albuminuria detectable by ordinary clinical tests is never functional. While the ultimate prognosis[3] in these cases appears to be almost invariably good, and about $\frac{1}{3}$ of the cases clear up after the age of 30, nevertheless, there may have been some temporary or underlying kidney damage. After a discussion of the extrarenal factors in albuminuria, Volhard[4] concluded that every albuminuria must be attributed to damage of the kidney epithelium. When we recall that chronic nephritis is the result of repeated injuries to the kidneys, and that the urine between acute exacerbations may be normal, we get a glimpse of possible harm in this apparently innocent disturbance.

An analysis[5] of the records of 3642 male students at this university showed that 26% had occasional and 6.4% persistent albuminuria, with no other evidence of kidney disease. Even if we concede those with only an occasional albuminuria to the class of individuals who during a physical examination show a slight elevation of blood pressure, an increased pulse rate, and perhaps a slight glycosuria without hyperglycemia, we still have the cases of persistent albuminuria to account for. The first group may be excused on the basis of vasomotor instability, but we cannot help wondering whether these repeated "functional" disturbances may not in time lead to organic changes in the kidneys, heart and bloodvessels.

Analysis of Cases. The present report is based on further analysis of 58 cases of persistent albuminuria and the application of 2 theories on the etiology of the abnormality. The ages of the students varied between 17 and 28. The heat and acetic acid test for albuminuria was used and the amount recorded ranged from a faint trace (1+) to a heavy cloud (4+). Occasional hyalin and granular casts were found in 20.3% of the cases. As to body weight, 17% of the

students were more than 10% overweight, while 21.2% were more than 10% underweight. The tonsils had been removed in 78.7% of the patients, while in 20.8% the tonsils were present and pronounced infected by the otolaryngologist. Only 1 student had a non-vital tooth, negative for abscess by Roentgen ray report. The blood pressure, taken in all of the cases, was never over 150 systolic. Only 5.1% had systolic pressures between 140 and 150. The average pulse pressure for the entire group was 50; 2% had a pulse rate over 90 and in 20% the rate was less than 70. Only 1 student had a moderate lordosis of the lumbar spine. Complete blood counts were done on all, with a normal result in every case. There were no hemoglobin estimations below 80%. All of the students were Mantoux-tested, and those with a positive reaction had chest roentgenograms, but no case of active tuberculosis was found. The past medical histories of the students were apparently irrelevant, as no disease or other abnormality occurred with unusual frequency. Scarlet fever had occurred in 20.7% and 13.3% of the students admitted "frequent" head colds, with about the same figures for a control[5] group. The family histories of the students showed cardio-renal disease in 1 of the parents in 12% of the cases, more than double that found in a control[5] group.

An orthostatic response to the albuminuria was present in 58.6% of the functional albuminuria patients. This was determined by having the patient completely empty his bladder immediately before retiring and then as soon as he awoke the next morning voiding a specimen while still in the recumbent position. In the cases with orthostatic albuminuria this early morning specimen was free of albumin.

The phenolsulphonephthalein test intravenously was done in 25 of the subjects, and the average total output of dye in 2 hr. was 70%. In 24% of the cases the total output for 2 hr. was between 80 and 88%. In 56% it was over 70% and in no instance was the total output less than 50%. The Mosenthal test on this same group showed that the night urine exceeded the day urine in 12.1% of the cases. In 30.3% the specific gravities of the day specimens varied more than 10 points, and in 50% it varied more than 7. In no instance was the variation in specific gravity less than 5 points.

Functional Albuminuria and Nephrosis. Since all attempts to prove these unexplained albuminurias as due to renal damage have thus far failed, it was thought that perhaps we were dealing with a temporary derangement of metabolism similar to Epstein's nephrosis (diabetes albuminuricus). It is now fairly well agreed that there exists a "nephrotic syndrome" characterized by general edema, marked albuminuria and lowered basal metabolism. This may be present in the absence of other evidence of kidney diseases (hypertension, arterial changes and impaired renal function), as shown by normal kidney excretion tests and blood values. The edema occur-

ring in nephrosis is believed due to the condition of hypoproteinemia resulting from loss of large amounts of protein as albumin in the urine.[6] The albumin excreted in functional albuminuria is usually small and probably rarely approaches the minimal amount of 1 gm. of protein per liter a day, which appears necessary to cause hypoproteinemia.[7]

A basal metabolism was done on all of our cases, and it was found that 80.9% had a minus rate (average, −7). A basal metabolic rate below −15 was present in 21.4% of the albuminurics as compared with 14% in 100 control basal metabolism determinations in male students of the same age group without albuminuria. Ten of the functional albuminuria patients with lowered basal metabolisms were given thyroid extract in doses of gr. ss, gradually increased to gr. i, 3 times a day for 2 weeks. In none of the cases was there any apparent change in the occurrence or in the amount of albumin.

Calcium in Functional Albuminuria. If we dismiss abnormal protein metabolism as the cause of functional albuminuria, and admit that albuminuria is not ordinarily due to foreign toxic proteins in the blood stream,[8] and that the plasma proteins of patients with albuminuria show no increased diffusibility,[9] one may attribute functional albuminuria to some form of renal injury, however mild and transient. Cushny[10] attributes albuminuria to alterations in the glomerular capsule which allows the passage of plasma proteins. It is well known that albuminuria can readily be produced by interrupting the blood supply of the kidney by compression of the artery or vein, or of the ureter which leads to pressure on the vein. The albuminuria in these experiments is due to asphyxia, which produces temporary damage resulting in increased permeability of the glomerular capsule[10] or of the glomerular capillaries.[11] It has also been demonstrated that vasoconstriction produced experimentally by adrenalin injections or increased adrenalin secretion causes albuminuria.[12] According to these views, functional albuminuria is probably the result of some form of pathologic physiology of the kidney, most likely an increased permeability of the glomerular tuft. It is well known that calcium diminishes the permeability of cell membranes and that this effect is not dependent upon the entrance of the salt into the interior of the cell.[13] Patients with nephritis, as well as patients with nephrosis, often show a hypocalcemia.

Normal blood values for urea, uric acid, creatinin, sugar and alkali reserve have been reported[14] in cases of functional albuminuria, but no reference is made to the serum calcium. The normal serum calcium values for adults is generally set between 9 and 11.5 mg. and for infants 10 to 11.5 mg.[15] Serum calcium determinations in normal boys,[16] between the ages of 8 and 20 years, were found to range from 7.6 to 12.5 mg.

The blood serum calcium was determined on 10 of the students with persistent functional albuminuria. The blood was obtained by venoclysis before breakfast and the amount of serum calcium present was determined according to the method of Clark and Collip. In the 10 cases examined, the serum calcium ranged between 10.5 and 12.2 mg. In 5 of the determinations the values were over 11.5 mg., *i. e.*, on the high side of normal.

The fact that the total blood calcium is normal or even high in cases of persistent albuminuria does not necessarily mean that the albuminuria may not be due to a deficiency of one of the calcium fractions. It has been shown[17] that calcium is present in the serum in at least 4 forms, 2 of which are diffusible and 2 non-diffusible. Of the diffusible calcium, about $\frac{2}{3}$ is in the form of an "adsorbable calcium-phosphorus complex" and the remainder contains the calcium. The "protein-bound" fraction of the blood calcium is of the non-diffusible form and the amount varies roughly with the total protein concentration, and so it is this form of calcium which is reduced in cases of nephritis and of nephrosis, and accounts for low values for total serum calcium in these conditions. On the other hand, certain diseases as adult human rickets, which show a normal or even high serum calcium, may have low values for the diffusible fraction, especially in the "adsorbable calcium-phosphorus complex."[17] Despite the finding of normal total serum calcium in cases of persistent functional albuminuria, it was thought advisable to try the effects of calcium ingestion. Calcium gluconate, in dram doses 4 times a day for 2 weeks, was given to 16 of the students with persistent functional albuminuria. The result was that in 5 (31.2%) of the cases there was no change in the condition, while 6 (37.5%) showed a definite decrease in the amount of albumin excreted, and in the remaining 5 (31.2%) there was a total disappearance of the albuminuria. In other words, 68.7% of the cases showed improvement or total disappearance of the albuminuria.

Further examination of the 5 "recovered" cases 1 year after their last dose of calcium showed that 4 of them still remained free of albuminuria.

Conclusions. 1. Nothing was found in the past medical histories or in the physical examinations of 56 otherwise healthy male students with persistent functional albuminuria to account for the urinary abnormality. The kidney function as determined by the phenolsulphonephthalein and Mosenthal tests was normal.

2. Cardiorenal disease in the parents of students with functional albuminuria was more than twice as frequent as in the parents of students showing no such abnormality.

3. A tendency to low basal metabolism readings was found in 80.9%, but in the 10 cases tested with moderate doses of thyroid extract there was no improvement in the albuminuria.

4. The blood serum calciums were normal in 10 students with persistent functional albuminuria, although calcium medication had a favorable influence on the albuminuria in 11 of 16 cases tried.

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THE RELATION OF NEGATIVE PRESSURE IN THE EPIDURAL SPACE TO POSTPUNCTURE HEADACHE.

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The examination of the spinal fluid has come to be recognized as an essential part of many general medical examinations. Its value is even more important when dealing with individuals known to have syphilis. It is well established that invasion of the central nervous system may begin soon after the appearance of the primary lesion and that physical examination and blood Wassermann tests are often insufficient to detect the presence of neurosyphilis. Many cases of syphilis (I refer particularly to the cutaneous manifestations of the disease) are discharged from treatment without knowledge of the spinal-fluid findings. I feel that many physicians are deterred from the use of this valuable diagnostic procedure for fear of the prolonged and disagreeable symptoms which may and often do follow lumbar puncture. Nelson[4] states that about 20% of the

lumbar punctures at the Mayo Clinic produce definite postpuncture reactions. Stokes[8] reports an incidence of 15 to 25% of headache produced in hospital patients. These figures seem very high when the test is conducted on patients who are hospitalized and at rest for 24 hours or more following puncture. It is obvious that such a high percentage of disagreeable reactions deters the physician's hand and tends to place the procedure in disrepute among his clientele. If the above figures may be accepted as typical of the incidence of postpuncture headaches in hospital patients, one wonders what the incidence is in ambulant patients.

The question of the substitution of cisternal puncture for lumbar puncture is as yet unsettled. It is my opinion that it cannot be recommended as a routine procedure and that patients have an innate fear of being "stuck in the head." I am sure that in the hands of a competent neurologist cisternal puncture is relatively safe; I am equally sure that it is unsafe in the hands of many men who must of necessity carry out examinations of the spinal fluid.

It is highly desirable and important that the technique of lumbar puncture should be brought to a point whereby it may be performed on ambulant patients with very little pain to the patient or the development of distressing or deleterious sequelæ. This paper outlines certain factors which tend to produce postpuncture headaches and describes a technique which has rendered feasible the performance of lumbar puncture on ambulant patients.

Causes of Postpuncture Headaches. It has been well established that the removal of spinal fluid in ordinary amounts and at ordinary speed does not result in postpuncture headache. The amount of fluid removed has very little to do with the degree of the reaction. Headache, vertigo and nausea are apparently due to persistent postpuncture leakage of spinal fluid through the needle hole in the dura. That such leakage does take place has been demonstrated by Ayer,[7] who injected lampblack into the cistern of cats. The lampblack was found at necropsy to be lying beneath the cervical muscles. Further proof for this view is adduced by Nelson,[4] who performed repeated lumbar punctures during and after postpuncture headaches. Careful estimations of pressure were made at the beginning and at the completion of the withdrawal of fluid. If headache developed, a third pressure measurement was taken during the course of the headache. The spinal-fluid pressures during the headache were found to be consistently lower than the pressure following completion of the original puncture. This may be taken as evidence of a further fall of pressure following withdrawal of the needle. It is obvious therefore that headache probably is to be avoided by preventing postpuncture leakage of spinal fluid from the dura. While such leakage is minimized by the supine position, it is evident that it is not eliminated. Let us examine a few of the factors which determine postpuncture leakage:

1. *The Size of the Needle.* Greene's[1,2] studies (1923) conclusively demonstrated that persistent leakage from the dura is due directly to the amount of trauma to the spinal dura sac. He further demonstrated that the rate of flow from the dural sac was directly proportional to the size of the hole made by the needle.

2. *Shape of Point.* Greene was able to demonstrate by microscopic examination of the dura that much greater trauma was produced in the membrane by the use of a needle with a blunt cutting point than by a needle of the same caliber with a sharp tapering point. The elastic and fibrous lamellæ of the dura run longitudinally and almost parallel. The pointed needle simply separates these fibers instead of cutting them and there is much earlier closure of such a wound. The above observations therefore suggest the use of a needle which should not be larger than 22- to 25-gauge.

The needle which I employ at present is a 22-gauge, 3½ inches in length, with a sharp, tapering point. The point resembles that of a cambric needle, and the opening is below the apex.*

The objection may be raised that a small needle is more liable to break. Exactly the contrary is true. A needle of this size may be bent at right angles, straightened and still be serviceable. Dr. Greene has very kindly presented me with a needle which he frequently tied in a knot and untied prior to performing a puncture. This needle has been used for the performance of about 500 lumbar punctures and was still entirely usable. Further objection may be raised that the flow from such a needle is too slow. This is easily obviated by attaching a 10-cc. syringe to the needle and aspirating the required amount of fluid. Many textbooks contain grave warnings against the aspiration of spinal fluid. Those of have had experience with the making of encephalograms know that this anxiety is ill founded. It is also true that in case of the development of symptoms suggestive of medullary pressure, the most satisfactory treatment would be replacement of the spinal fluid which had been withdrawn. If this is under control in the syringe this may be readily and quickly done.

An additional advantage of the small needle is that it is flexible enough to move freely with the dura. Any accidental movement of the head produces an up-and-down movement of the dural sac in the bony canal. If a rigid needle is used, being fixed by two points of attachment (skin and interspinous ligament) it is unable to bend. As a result, the dura saws over the needle with each movement of the head with resultant enlarging of the needle opening and greater oppportunity for postpuncture leakage. It is needless to say, of course, that the small needle produces much less trauma to the skin and ligament and is therefore less painful to the patient. If the needle is falsely directed in the first attempt, additional punctures

* Such a needle may be obtained from Becton Dickinson & Co., Rutherford, N. J. (No. 460 LNG).

may be made without undue discomfort to the patient. If the patient is extremely muscular, an 18-gauge needle may be passed through the skin and interspinous ligaments following the application of novocain. The small needle will then readily follow the track of the 18-gauge needle.

Results of Use of Proper Needle. All observations recorded in this discussion were made on ambulant patients examined by the Division of Medicine or of Neurology at the Wheeling Clinic. These candidates for puncture report to us at 9 A.M. They remain at the Clinic in bed until 4 P.M. At this time they are allowed to return home, employing various means of transportation which vary from a long walk to a trip by railroad, bus or automobile. The distance which individual patients travel varies from a few blocks to 50 miles. Obviously, such patients cannot follow the dictum of Stokes.[8] "After the patient lies down following the puncture, he should not sit up again for at least 24 and preferably 48 hr." The adoption of the needle as described above reduced the incidence of postpuncture headaches in our patients from approximately 10 to 5%. However, if lumbar puncture were to be made as often as indicated on ambulant patients, it became imperative to reduce the incidence of headache still lower.

Observations Leading to Further Reduction in Postpuncture Headaches. 1. The appearance of a drop of spinal fluid on the skin following the withdrawal of the needle.

2. In punctures in which some difficulty is experenced in entering the dural sac, or if for any reason the stylet was withdrawn from the needle before the dural sac was entered, we often noted a slight but distinct hissing sound as if there were a sudden inrush of air into the needle.

3. We have observed that if the needle is slowly withdrawn following successful puncture that the drop of fluid in the hub of the needle was sometimes aspirated inward. This seemed to occur just after the needle point emerged from the dura.

4. Strangely enough, the punctures which were performed with the greatest ease were apparently the ones which lead most frequently to postpuncture headaches. In other words, punctures which were accomplished with one simple advancement of the needle, resulted more frequently in postpuncture reaction.

We were at a loss to explain or to correlate these isolated observations until the publication of the excellent work of Heldt and Maloney.[3] These workers, having noted the same phenomena, concluded that a condition of negative pressure existed in the epidural space, somewhat comparable to the negative pressure existing in the pleural spaces. The development of such a negative pressure was believed to be due to late embryonic and early fetal extension of the vertebral column. The more rapid growth of the bony struc-

tures produces a caudal elongation of the vertebral canal away from the conus terminale of the slower growing, encephalad fixed cord. They found this negative pressure to vary from −1 to −18 mm. of mercury. We have constructed a manometer similar to their model and have been able to confirm their findings in certain individuals (14 patients in this series). The amount of negative pressure in the epidural space varies greatly and probably is not present in all patients. We have no explanation for this apparent variation. Two statements may be made in regard to the measurement of this pressure. If the needle is advanced too far and impinges on the dura without puncturing it, a false negative pressure will be registered as the epidural space is increased by the forward pressure on the dura. Second, we have not been able to demonstrate negative pressure in individuals who have had multiple lumbar punctures. It is probable that the degree of negative pressure in the epidural space is affected by, (1) the amount of spinal fluid present, *i. e.*, the expansion or contraction of the dural sac; (2) filling and emptying of the epidural veins with change of posture. If the presence of a negative pressure in the epidural space may be assumed as seems justified by the observations of Heldt and Maloney, and our own observations, it is obvious that the opportunity for leakage to occur depends upon the balance of the pressure existing in the subdural and epidural spaces at the needle opening. Negative epidural pressure would tend to aspirate fluid through the dural opening no matter how small this opening may be and such aspiration might be expected to continue until an equalization of pressure was established. So long as such leakage continues, postpuncture headache might be expected, from small but steady withdrawal of fluid from the subdural space. It should be pointed out also that the withdrawal of fluid from the spina dural sac decreases the space occupied by the spinal membranes, thereby increasing the volume of the epidural space with a resulting increase in negative pressure.

Prevention of Postpuncture Headaches Based Upon the Above Observations. Nelson[4] advises the plugging of the dural opening with a strand of catgut inserted by a very ingenious instrument which he has devised. This has also been attempted by Heldt and Maloney[5] with success so far as the obviation of headache is concerned. However, the use of the catgut has resulted in rather severe reactions marked by rise in temperature and disagreeable leg pains.

Remembering our observation that the easy punctures produce the most headaches, we concluded that the repeated withdrawal of the stylet during the more difficult punctures allowed the outside air to pass through the needle to the epidural space, thereby raising the pressure in that region at least temporarily to atmospheric figures. We have therefore made it a practice to halt the needle in the epidural space during each puncture and allow it to remain *in*

situ with the stylet removed. The puncture is then continued in the usual way. On completion of the puncture the stylet is not replaced but the needle is withdrawn again into the epidural space. It is allowed to remain there for 30 sec. before being pulled out through the ligaments. It is our belief that the air thus allowed to enter the epidural space serves temporarily at least, as a cushion against the leakage of fluid from the dural sac.

Since we have adopted: (1) The use of a needle not greater than 22-gauge with a sharp tapered point; (2) the practice of slow withdrawal of the needle with full time allowance for the entry of air to the subdural space, we have been able almost completely to obviate the complication of severe postpuncture headache. In the last 100 examinations done on ambulant patients, 3 have complained of slight headaches the day following puncture. These were not severe and did not necessitate the patient giving up his or her usual daily activities. We consider this a reduction of the incidence of postpuncture headaches to less than 3%. The morbidity in this series is so slight that it may be disregarded.

Summary. 1. The more frequent examination of the spinal fluid, especially in suspected syphilis, is advocated.

2. A review of the literature, combined with our own confirmatory observations, strongly suggests that continued leakage of spinal fluid from the dural sac is the predominant cause of postpuncture headache. This continued leakage may be obviated by: *a*, use of needle not larger than 22-gauge with a sharp tapering point; *b*, the elimination of the negative epidural pressure, shown by manometric readings to exist in at least some individuals. This is accomplished by allowing an inflow of air through the needle while the point rests in the epidural space.

3. The observance of the precautions mentioned above has resulted in marked reduction in the incidence of postpuncture headache in our series (from 10% to 3%). This has been accomplished despite the fact that puncture is performed regularly on ambulant patients.

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THE EFFECT OF NON-SEDATIVE DRUGS AND OTHER MEASURES IN MIGRAINE.*

WITH ESPECIAL REFERENCE TO ERGOTAMIN TARTRATE.

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THE excellent review of Riley[1] has so completely covered the subject of migraine that an extensive survey is unnecessary at this time. Like the convulsive state, migraine is a symptom complex due to a number of causes. Allergic reactions, hormonal imbalance, water retention and instability of innervation of the meningeal and cerebral vessels have been regarded as etiologic factors. At present, most students of the subject believe that a vascular spasm in the meningeal and cerebral vessels forms the pathophysiologic basis.

To evaluate the results of the drug actions to be described, it is necessary to understand the vasomotor innervation of the cerebral circulation. Direct photomicrography has demonstrated vasomotor control of the cerebral circulation (Forbes and Wolff[2]), and the pathway in cats and monkeys has been traced by Cobb and Finesinger[3] and Chorobski and Penfield.[4] Stimulation of the proximal end of one vagus nerve induces *bilateral cerebral vasodilatation—a parasympathetic action*, whereas *stimulation of the cervical sympathetic causes ipsolateral vasoconstriction* of pial vessels.

In the following study we have investigated the effects of non-sedative drugs and other measures in a group of individuals suffering from typical long-standing, severe and intractable migraine. The medical, neurologic, nasal and serologic examinations were entirely negative. The basal metabolic rates and roentgenograms of skull and nasal sinuses were normal. There were 19 women ranging in ages from 19 to 64 (average, 37) and 6 men from 36 to 48 (average, 42). The duration of the disease in both groups averaged 21 years. The headaches occurred from 2 to 12 times a month. Menstruation was a provocative factor in 13 of the 19 women.

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The effects of the various measures are summarized in Table 1. Hypodermic medication was used to avoid the uncertainties attending gastro-intestinal absorption.

TABLE 1.—THE RESULT OF VARIOUS MEASURES IN THE PRODUCTION AND RELIEF OF MIGRAINOUS HEADACHE.*

Measure used.	Relief.	Doubtful.	No relief.	Intensification.	Headache.	
					Produced.	Not produced.
Hyperpnea	.....	....	.....	....	....	13 (11 F)
	.....	....	.....	....	....	3 (2 M)
Subcutaneous injection						
Follutein	.....	....	.....	....	4 (4 F)	11 (8 F)
						2 (2 M)
Pitressin	.....	....	1 (1 F)	....	....	4 (4 F)
Insulin	.....	....	.....	....	1 (1 F)	18 (11 F)
						1 (1 M)
Histamin	.....	....	5 (4 F)	3 (3 F)	4 (3 F)	5 (3 F)
Adrenalin	2 (2 F)	....	3 (3 F)	1 (1 F)	....	3 (3 F)
						1 (1 M)
Ephedrin	2 (2 F)	....	6 (4 F)	1 (1 F)	....	1 (1 F)
Ergotamin tartrate	27 (11 F)	....	3 (2 F)	....	....	.....
	7 (3 M)	....	2 (2 M)	....	....	.....
Mecholin	6 (4 F)	....	4 (4 F)	....	1 (1 F)	
					1 (1 M)	1 (1 F)
Amniotin	2 (1 F)	....	15 (3 F)	1 (1 F)	3 (2 F)	.....
Tissue Extract 568	3 (3 F)	....	3 (3 F)	1 (1 F)	1 (1 F)	1 (1 M)
Caffein sodium benzoate	.....	....	4 (4 F)	....	....	.....
	.....	....	2 (2 M)	....	....	.....
Amyl nitrite (by inhalation)	2 (2 F)	....	3 (3 F)	....	....	.....
	.....	....	1 (1 M)	....	....	1 (1 M)
Calcium gluconate (by intravenous injection)	2 (2 F)	3 (3 F)	3 (3 F)	....	....	.....
	.....	....	1 (1 M)	....	....	.....

* The numbers refer to the number of experiments. F = woman; M = man.

Hyperpnea. Since migraine bears a well-known relationship to the convulsive state, it is natural that hyperpnea which induces convulsions in about 40% of epileptics should be used to provoke headache. Muck[5] investigated 27 cases of migraine and found that the headache could be produced in those individuals who gave a positive reaction to adrenalin applied to the nasal mucous membrane.

In our series, 11 women were subjected to 13 hyperpnea tests and 2 men to 3 tests without the appearance of headache. The period of overventilation lasted 8 to 10 minutes. The patients complained of uncomfortable tingling and numbness in the extremities and showed positive Chvostek sign; 1 woman developed tetanic spasms. The adrenalin test described by Muck was not used in this series.

Follutein (or Antuitrin S). This preparation contains 2 of the hormones of the anterior lobe of the pituitary gland—an ovarian follicle-stimulating hormone (Prolan A) and a luteinizing hormone (Prolan B). Riley, Brickner and Kurzrock[6] found prolan in the urine before or during a migrainous headache in 20 of 29 instances. They injected 2 cc. of follutein intramuscularly in 9 women and were able to produce a characteristic headache in 7, in 4 to 12 hours. In 1 of 2 men the injection of follutein induced a headache. We injected 1 cc. of follutein subcutaneously and produced the typical headache in 4 women, but failed 11 times in 8 other women. Follutein in 1-cc. dosage failed twice in 2 men.

Pitressin. This is a hormone derived from the posterior lobe of the pituitary gland. It has proven useful in diminishing the urinary output in cases of diabetes insipidus. Forbes and his coworkers[7] have shown that local intravenous injections of pituitary extract and pitressin cause dilatation of the pial arteries in anesthetized animals in 65% of the cases and constriction in 19%. Pitressin is believed to promote water retention in tissues. Földes[8] believes that migraine is due to increased water retention in meningeal and cerebral tissues.

We injected 1 cc. of pitressin in 4 women and at the same time forced fluids. No headaches resulted. In 3 of the cases increased retention of water was not actually proven.

Insulin. An attempt was made to produce the headache by the injection of insulin. In 11 women and in 1 man, 19 injections of 10 or 15 units failed to produce the headache in the fasting subject; in 1 woman a headache was induced. Apparently a state of low blood sugar is not an important cause of migraine.

Histamin. This is beta-iminazolyl ethylamin. According to Sollmann,[9] histamin causes an extensive fall of blood pressure due to capillary dilatation. It acts on the vessel wall with an effect opposite to that of adrenalin. One-half cubic centimeter of 1 to 1000 histamin phosphate was injected and its effect noted for a period of 3 hours. In 4 women it afforded no relief 5 times. In 3 women the headache was intensified. In 3 other women headaches were produced on 4 occasions; in 3 women it failed to produce headache 5 times. Since histamin is a capillary dilator, one would expect that it might help those individuals whose headaches were relieved by ergotamin tartrate, the action of which is also believed to be one of vasodilatation, dependent upon sympathetic paralysis. However, injections of ergotamin tartrate eased the headache in 1 woman on 9 different occasions, whereas in the same patient histamin failed twice to affect the headache, and the third time made it worse. Another woman was benefited on 2 occasions by ergotamin tartrate but was not relieved by histamin.

Adrenalin. Forbes, Finley and Nason[10] have shown that the intravenous injection of adrenalin causes a rise in general blood

pressure and a secondary dilatation of the pial bloodvessels in cats and monkeys. When adrenalin is applied locally to the surface of the brain it induces a more or less mild vasoconstriction. In our cases, 1 cc. of a 1 to 1000 adrenalin solution was injected. In 6 women it helped twice and failed 3 times; in 1 woman the headache was intensified. In 3 women and in 1 man no headache was produced by the end of 1 hour. In 1 woman relief was obtained twice, but similar benefit also followed the injection of the vasodilator, ergotamin tartrate. In another woman, ergotamin tartrate was ineffective. In 2 other instances, ergotamin tartrate was effective, whereas adrenalin failed. The relationship of these 2 drugs will be discussed below.

Ephedrin Sulphate. In 2 women an injection of 1 cc. of ephedrin sulphate (gr. $\frac{3}{4}$) gave relief, but in 4 other women 6 headaches were unaffected. In 1 woman the headache was intensified; in another it failed to induce headache. In 1 of the women relieved by ephedrin the headache was also favorably influenced by ergotamin tartrate. However, 3 headaches in 1 woman were unaffected by ephedrin and a 4th was made worse; the same woman was completely relieved on 4 different occasions by ergotamin tartrate.

Ergotamin Tartrate (*Trade Name, "Gynergen"*). This is one of the alkaloids of ergot which was isolated by Stoll,[11] in 1918, in crystalline form. Dale[12] pointed out that there was a "specific pharmacologic antagonism" between ergotoxin and adrenalin. Ergotoxin paralyzes the sympathetic augmentor functions stimulated by adrenalin. *Ergotamin* paralyzes both the motor and inhibitory endings of the sympathetic nervous system according to Rothlin,[13] and bears the same relationship to the sympathetic system that atropin bears to the parasympathetic.

Ergotamin tartrate has been used in the treatment of migraine for a number of years. Tzanck,[14] in 1928, noted improvement in 8 subjects; 2 of 3 sufferers from status migrainosus were reported as "almost cured." Trautmann[15] described favorable results in the treatment of 30 patients. Kottmann[16] reported improvement in 5 patients with sympathicotonic features. He noted also that subcutaneous injection had a more intense and beneficial effect than oral administration. He stressed the involvement of the vegetative nervous system in migraine, and reëmphasized the grouping of migrainous subjects into sympathicotonic and vagotonic types. By the successful use of ergotamin tartrate, Kottmann believes that one can isolate the sympathicotonic group from other types of migraine which are unbenefited by this drug.

In this series, 11 women were benefited 27 times and 3 men, 7 times. Two women were not relieved during the course of 3 headaches and 2 men were not helped in 2 headaches. At no time was a headache made worse. Headaches once removed by this drug were always eased by it; if the drug failed on the first injection,

it was ineffective on future trials. Injection of 0.5 (0.25 mg.) to 1 (0.5 mg.) cc. of ergotamin tartrate caused the headache to disappear in 1 to 3 hours. Vomiting frequently accompanied relief. Ergotamin tartrate may be given orally in pill form in 1-mg. dosage. In our experience, subcutaneous was more effective than oral administration. At times the taking of 1 mg., 2 to 4 times a day by mouth, during the symptom-free interval lessened the frequency and severity of the attacks. In 1 of our cases in which benefit occurred, the discontinuance of the drug precipitated a very severe headache. This seemed comparable to the outbreak of convulsive seizures when phenobarbital is suddenly stopped after prolonged usage.

Acetylcholin and Mecholin. Loewi[17] first demonstrated the action of the vagus hormone in 1921. He showed that vagus stimulation of a frog's heart liberated a substance which entered the perfusing solution. This perfusate was capable of stimulating a second frog's heart in a vagotonic manner. The name, "Vagus-Stoff" was given to this hormone which is the direct antithesis of the sympathetic hormone—adrenalin. The vagus hormone is acetylcholin or a very closely allied compound. Acetylcholin is very rapidly disintegrated in the body. Simonart[18] isolated a more stable compound, the acetyl ester of betamethyl cholin (mecholin). Wolff[19] observed dilatation of the cerebral arteries, veins and minute vessels in the cat after the intravenous injection of acetylcholin. When subcutaneously injected in man in 15-mg. dosage, mecholin produced a striking reaction, characterized by flushing, salivation, lowering of blood pressure, with rise in the pulse rate. The tachycardia seemed to be a compensatory phenomenon offsetting the low blood pressure.

In 4 women 6 headaches were relieved very promptly; in 4 other women it was ineffective 4 times. It produced headaches in a man and in a woman on 2 occasions, and once it failed to induce headache in a woman. In our most intractable case of migraine, injection of mecholin produced immediate and remarkable relief on 3 occasions after many other measures had been unsuccessfully tried. Though relief is almost immediately attained, the headache is apt to reappear after $\frac{1}{4}$ to $\frac{1}{2}$ hr. as the action of the drug wears off.

Parasympathetic (vagus) stimulation induced by mecholin has not the same effect as regards the headache as sympathetic paralysis believed to be produced by ergotamin tartrate. For we have seen instances in which mecholin failed to relieve headaches in an individual invariably relieved by ergotamin tartrate. Moreover, in a man benefited by the latter, mecholin at one time produced a headache.

Amniotin. This is the estrus-inducing or ovarian follicular hormone. Amniotin is prepared from fetal amniotic fluid. One cubic centimeter (equalling 50 rat units) was the dose used in this series.

One woman was relieved of 2 headaches, but it failed in 3 other women on 15 occasions. In 3 women it produced a headache or intensified one on 4 occasions. Since Riley, Brickner and Kurzrock[6] demonstrated the deficiency of this hormone in the urine of women suffering from migraine, before and during the headache, one might expect its administration to have a beneficial effect in prevention. However, this has not occurred even when the hormone was given repeatedly over a number of days. Indeed, in 1 woman, 5 cc. (250 rat units) produced a headache on 1 occasion and 2 cc. (100 rat units) on another.

Tissue Extract 568. This is a pancreatic derivative which is said to contain neither histamin nor cholin in sufficient quantities to explain its physiologic action. According to Wolffe and his coworkers,[20] it is said to have a vasodilator effect contrary to that of adrenalin. It is standardized in terms of units (10 units to 1 cc.). One unit of tissue extract is said to neutralize the pressor effect of 1/1000 mg. of adrenalin. It was administered in doses of 3 cc. subcutaneously (30 units), with the following results: In 3 women, 3 headaches were relieved; in 3 other women there were 3 failures; once it did not produce a headache in a man, but on another occasion it provoked a headache in a woman. Once a headache was intensified in a woman. In 1 woman unrelieved by mecholin, relief was gotten from tissue extract though the headache reappeared the next day. In a man in whom mecholin produced a headache, tissue extract failed to induce one.

Caffein Sodium Benzoate. It has been known that there is no increase in intracranial pressure during a migrainous headache, hence no benefit may be anticipated from the use of drugs which decrease intracranial pressure, such as caffein. Four women and 2 men were unrelieved of their headaches by the subcutaneous administration of this drug, in dosage of gr. viiss.

Amyl Nitrite. Inhalation of this drug produces a rapid though transient rise in intracranial pressure. Wolff[21] observed dilatation of the cerebral vessels in the cat following inhalation of this drug.

Relief was obtained in 2 women but not in 3 others. It did not relieve a man and once failed to produce a headache in a man.

Calcium. The calcium-potassium balance is said to have an influence on the normal action of the vegetative nervous system. Potassium is an adjuvant to the parasympathetic, and calcium to the sympathetic nervous system. If some cases of migraine are due to the overaction of the sympathetic nervous system, the administration of calcium might be expected to increase the headache. In our series, calcium gluconate (10 cc. of a 10% solution containing 9.3% of the calcium ion) was used intravenously. Two women were benefited twice, 3 others were given doubtful relief; in 3 others no favorable effect was noted; this was also true in 1 man. One woman was helped on 1 occasion and partially relieved

on another; she was repeatedly aided by ergotamin tartrate. In a man and a woman unbenefited by calcium, ergotamin tartrate was successful.

Summary. To the investigator of so paroxysmal a disorder as migraine, the ability to *induce* the headache by artificial measures is an important time-saving factor. In this series no consistent provocative measure was found. Follutein, histamin and large doses of amniotin were sometimes successful.

In the *relief* of the headache, the most striking benefit was obtained by the hypodermic injection of ergotamin tartrate, a drug which is believed to produce vasodilatation by paralyzing the sympathetic innervation. However, such action on the human cerebral circulation has not been proven. Measures supposed to induce vasodilatation of the cerebral vessels did not give invariable relief. Thus mecholin, a parasympathetic (vagus) stimulant did not always prove helpful, though it gave striking relief in a few cases unaffected by ergotamin tartrate. Histamin was observed to produce cerebral vasodilatation in a man during the course of a cerebral operation (Weiss, Robb and Ellis[22]), yet it was not of benefit in our series; indeed, this drug was more apt to intensify or provoke the pain. Amyl nitrite, another vasodilator, failed more often than it brought relief. Adrenalin also was often of no benefit. While adrenalin causes dilatation of the pial bloodvessels in animals as a secondary result of the rise in blood pressure, we do not know what effect subcutaneous injection of this drug has on the human cerebral circulation.

The administration of the ovarian follicular hormone, which is known to be lacking in women with migraine, did not give the expected results. The injection of intravenous calcium was also more or less ineffective.

The diversity of results points to the presence of more than one pathophysiologic mechanism in the production of migrainous headache. One is led to believe that vasospasm is probably a secondary effect of, and not a primary factor in migraine.

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NUCLEOPROTEIN AND SPECIFIC TOXIN DERIVED FROM STREPTOCOCCUS SCARLATINÆ FILTRATE. THEIR SKIN REACTIONS, CHEMICAL AND IMMUNIZING PROPERTIES.*

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This work was begun for the purpose of studying the pathogenesis of nephritis produced experimentally by toxins of the Streptococcus scarlatinæ. In order to counteract the comparatively high resistance possessed by experimental animals against the streptococci, various concentrates from the sterile filtrate were injected. Following the injection of certain of the concentrated products, extreme degenerative nephritic lesions were produced in which destruction of tubular epithelium and complete loss of many glomeruli were the outstanding features. Productive glomerular changes were never encountered. The tubular changes were so intense as to suggest the presence in the injected material of toxic substances

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other than that of the specific toxin. The character of these associated toxic substances was revealed when comparable pathologic changes were produced by injection of similarly concentrated products of the uninoculated broth. Protein decomposition products, such as peptones, proteoses, albumoses, etc., occurring in the media and precipitated with the bacterial toxins in the course of the concentration procedures can produce *per se* pathologic changes in the kidney and other parenchymatous organs which simulate lesions due to the toxins alone.

The presence of such non-specific proteins, in our opinion, militates against the assay of toxicity of the bacterial products of the Streptococcus scarlatinæ by lethal dosage and handicaps the use of such products experimentally or clinically. We, therefore, deemed desirable the removal of such associated non-specific products as far as possible, from the toxin, before attempting the production of scarlatinal lesions or determination of the lethal dose of the toxin.

Although successful production of scarlatinal renal lesions comparable to those found in the human have been reported with the toxins of the Streptococcus scarlatinæ by Duval and his associates,[1] their findings have not been confirmed by Birkhaug and Howard[2] nor by our experiments.

Technique. Two strains of hemolytic streptococci were used for most of our experiments. One of these (No. 543) was a strain isolated by Dick and Dick and procured from the American Type Culture Company of Chicago in 1929. The second strain was isolated at the Children's Hospital from a postscarlatinal mastoiditis. Six days after exposure to this organism during experimental work, one of us (M. L. M.) developed a typical case of scarlet fever. The toxin from these 2 strains was, as far as could be determined, of equal toxicity. A third strain obtained through the kindness of Dr. Gladys Dick, in 1931, was also employed in later experiments. The medium used was a hormone broth containing 1% peptone and titrated to pH 7.5. In some cases 0.5% gelatin was added, but as this increased the time required for filtration of cultures, its use was discontinued.

To insure optimal aëration, 250 to 300 cc. of broth were placed in 1-liter flasks, inoculated and shaken frequently. Incubation for 5 days gave on fractionation a good yield of specific toxin but very small amounts of the nucleoprotein. Ten to 14 days' growth increased the yield of nucleoprotein, but was not so favorable for specific toxin production. In most experiments the incubated broth, after 5 days' incubation, was allowed to stand overnight. The upper clear supernatant fluid was decanted off and filtered successively through Berkefeld filters V and N. Culturing of such filtrates demonstrated their sterility. The various methods used for the purification and concentration of the toxins have been recently reviewed by Wadsworth and Quigley.[3] The outstanding agents employed have been ammonium sulphate, acetic acid, a combination of these two, alcohol in varying concentration and acetone, all of which have been tried by us. In the first series ammonium sulphate in half saturation was added to the filtrate, and the precipitate removed (Precipitate I). To the remaining filtrate additional ammonium sulphate was added to saturation and the resulting precipitate removed (Precipitate II). These 2 precipitates were further purified by reprecipitating twice and by dissolving in a minimal amount of distilled water and reprecipitating with 3 volumes of 95% alcohol. The

addition of 2 volumes of alcohol to the filtrate from Precipitate I resulted in the further formation of a heavy white precipitate, but this had little skin reddening property. Similar treatment of filtrate from Precipitate II resulted in a cloudiness only.

The best results were obtained by precipitation with alcohol in a manner similar to that described by Ando.[4] Acetone precipitations were consistently darker and greater in quantity. When the medium contained gelatin, the nucleoprotein was first removed by precipitation with acetic acid at pH 4 and centrifugation. The supernatant filtrate was neutralized to approximately pH 7 and varying amounts of 96% alcohol then added with stirring. The resulting precipitates were removed by centrifugation. Two volumes of alcohol sufficed to remove the major part of the toxic material as a skin reaction could not be elicited with the filtrate remaining after the removal of this precipitate. The bulky precipitates obtained with larger amounts of alcohol contained little additional specific protein. The average amount of toxin obtained with 2 volumes of alcohol was 0.3 gm. per liter of filtrate. Variations in amount depended mainly on length of incubation. Minimal amounts were obtained with 48 hr. and optimal with 5 to 6 days' incubation. The crude toxin was concentrated and reduced in volume by taking advantage of the greater solubility in water possessed by it than by the associated contaminants. The crude toxin was extracted with 200 cc. of distilled water per liter of original filtrate. Any undissolved material remaining was removed and dissolved in dilute acetic acid and designated fraction B. The aqueous extract after removal of fraction B was acidified with acetic acid (1 to 3) to pH 4, and the resulting white precipitate, designated as nucleoprotein, removed by centrifuging. The remaining filtrate was neutralized to pH 7 and precipitated with 2 to 1 alcohol. This white precipitate contained the bulk of the specific toxin. Refractionation was repeated 3 times in order to obtain a uniform product. When gelatin-enriched medium was used, the initial addition of acetic acid to pH 4 gave a bulky precipitate which contained not only the nucleoprotein but also many proteins derived from the gelatin. Neutralization of the filtrate resulting after centrifugation and subsequent treatment with alcohol, as outlined above, gave a specific toxin as in the gelatin-free filtrates. The final white precipitate was dried *in vacuo* and averaged 300 mg. per liter. This material gave a positive skin test in susceptible humans when 0.1 cc. of a 1 in 2500 solution or 0.04 mg. was injected intracutaneously. Subsequently the potency was increased to an intracutaneous dosage of 0.1 cc. of 1 to 3400 dilution by more rapid and careful chemical fractionation and drying. By the above chemical manipulation there is a considerable loss of toxin with reduction in solubility. Attempts to concentrate both the original filtrates and the concentrated toxins by means of adsorption with gum arabic, magnesium hydroxid and aluminum hydroxid at various pHs gave evidence of adsorption on the first 2 materials, but the degree of purification was not sufficiently satisfactory to justify further immediate work.

Pregl's micromethods were used in the determination of carbon, nitrogen, hydrogen, ash and phosphorus in the 3 fractions, viz., nucleoprotein, specific toxin and Fraction B. Samples weighing 4 to 6 mg. were used for all analyses.

In addition to the above analyses, optical rotation, reducing sugars, sulphur and moisture were determined on the specific toxin.

For the optical activity 100 mg. of the sample were dissolved in 10 cc. of water and the optical rotation measured in a standard saccharimeter.

Reducing sugars were determined by titration of a known quantity of hydrolyzed solution against Benedict's reagent. Hydrolysis was carried out in 20% hydrochloric acid for 12 hr.

Because of the high phosphorus content of fraction B, it was analyzed for calcium by precipitation of calcium oxalate.

The nucleoprotein fraction was tested for reducing sugar and optical rotation in the same manner as for the specific toxin.

Results of the microanalyses made on the 3 concentrated fractions derived from the filtrate are detailed in Table 1. The nitrogen content (13.53%), solubility characteristics and isoelectric point at approximately pH 4 of the nucleoprotein fraction indicates a typical protein. The low phosphorus and absence of a significant amount of reducing sugar after hydrolysis of the nucleoprotein is probably due to a certain amount of hydrolysis, despite precautions against this. Its group antigenic specificity (discussed later) strongly indicates that it forms an essential part of the streptococcic cell. It gave a positive skin reaction when 0.1 cc. of a 1 to 10,000 concen-

TABLE 1.—ANALYSIS OF 3 FRACTIONS SEPARATED FROM FILTRATE.

	Nucleoprotein, %	Fraction B, %	Specific toxin	
			Preparation 1 %	*Preparation 2* %
Nitrogen	11.56	5.19	6.86	5.45
	13.49	5.33	6.91	5.75
	...	...	7.58	5.76
Carbon	27.91	8.07	35.86	38.98
	31.71	10.70	36.56	39.20
Hydrogen	3.93	4.10	5.33	6.40
	4.54	4.34	5.77	6.65
	...	4.47		
Ash	6.11	51.01	5.54	3.44
	6.50	51.03	5.92	3.50
	...	51.17		
	...	Chiefly $Ca_3(PO_4)_2$		
Phosphorus	0.65	11.52	1.58	
	0.68	11.71	1.64	
		11.72		
Sulphur	...	...	0.30	
Reducing sugar	Trace (after hydrolysis)	...	9.50 (after hydrolysis)	
Specific rotation	$[\alpha]_D^{20} = -36°$		$[\alpha]_D^{20} = +20.8°$	

tration was injected intracutaneously in most older individuals. Fraction B, which consisted mainly of acid calcium phosphate associated with both protein and carbohydrate material, was inert on intracutaneous injection. The calcium was largely derived from the medium. The specific toxin corresponds to a glycoprotein, in which the protein is conjugated with a stable sugar group. It is heat-stable and only loses its specific activity after boiling for 1½ hr. No deterioration in the activity of the dried preparation has been found at the end of 3 years. By the method of purification used, the solubility in water and saline of the skin-reddening toxin of the

Streptococcus scarlatinæ was considerably decreased and the potency was much diminished. This observation is in agreement with Ando. Following precipitation by salts, alcohol or acetone, there was a decrease in solubility which was marked if allowed to stand in contact with the precipitating reagents too long. Rapid manipulation was found to be advisable for a high degree of recovery of the readily dispersed protein. Inasmuch as the rate of distribution and physical reactions *in vivo* are conditioned by the degree and ease of dispersion, this factor is considered an important one.

Preliminary standardization of the concentrated toxin on young white pigs, as recommended by Rosenow,[5] was tried. Considerable variation was noted in different individual animals, some failing to give any response whatever. Suitable animals were roughly $\frac{1}{10}$ as susceptible as the human, and the reaction appeared in 5 to 8 hr. Because of the comparatively low sensitivity of the pig's skin, final standardization had to be made on human subjects. The variation in activity between successive preparations of the toxin was so slight that this preliminary test was not found to be of any advantage. The final standardization was checked against the commercial "Dick" toxin on susceptible and non-susceptible individuals.

Susceptibility tests were made on 319 children up to the ages of 15 at the Children's Hospital, Presbyterian Home and Roselia Home for Foundlings. Intracutaneous injections of 0.1 cc. of commercial Dick toxin, of the concentrated specific toxin diluted 1 to 3400 in saline, and of the nucleoprotein in a dilution of 1 to 10,000 in saline were made. The results with the nucleoprotein are interesting because of the increased percentage of positive reactions obtained with increasing age. Up to 6 months of age, 17.7% positive reactions were found with a rapid increase to 77.8% at the end of the 1st year. After 4 years of age practically all individuals tested gave positive reactions. Varying degrees of redness with edema were observed with the nucleoprotein test.

Positive tests with the specific toxin paralleled those of the Dick test in 95% of the cases. The 5% consisted mainly of positive Dick reactions with negative specific toxin, and can probably be accounted for by the fact that much of the non-specific protein had been removed from the specific toxin. A very small number of cases gave a negative Dick with a positive specific toxin. Slight differences in concentration may account for this discrepancy. The tendency of the Dick reaction to exhibit a slight edema which is generally lacking with the specific toxin we are inclined to attribute to the presence of small amounts of nucleoprotein in the former.

The incidence of susceptibility to scarlet fever at different ages as indicated by our tests with the specific toxin varied considerably in the 3 institutions. This variation depended largely upon the exposure of the inmates to infection. The average percentage of

positive tests for the first year was 8% and no reactions were obtained during the first 6 months of life. There was a rapid rise to 42% during the second year, with a gradually increasing incidence reaching 72% in the 5th year. This was followed by a gradual decline to 27% in the 15th year.

Besides the tests made on the patients at the Children's Hospital, susceptibility reactions of the personnel were also made. The difference in the reactions found in the group of 113 individuals, consisting of resident physicians, nurses and laboratory staff, compared with those of the 60 employees, is interesting. In the former, 47 (41.6%) were negative and 66 (58.4%) were positive. Of the 47 negative reactors, 21 gave a history of scarlet fever. Among the group of 60 employees, only 1 reacted positively, and this individual, a girl aged 20, developed scarlet fever 2 weeks after the test was performed. Only 9 of the 59 originally negative gave a history of scarlet fever.

Attempts to immunize 34 of the 66 positive reactors of the staff group resulted in producing a negative reaction in 20 (58.8%). Of the 34, 16 were immunized with the commercial Dick series of 5 graded doses and after the fifth dose 7 (43.8%) remained positive. The reaction was not altered by a 6th dose. The 2d group of 18 were immunized with 5 doses of specific toxin of increasing intensity comparable to the Dick series. After the 5 doses, 7 (38.9%) remained positive. The reaction was not altered by a 6th dose. Three of these 7, however, became negative after 8 to 10 weekly small doses ($\frac{1}{4}$ to $\frac{1}{10}$ of the 1st immunizing dose). The positive reactors gave reactions with toxin boiled $1\frac{1}{2}$ hr.

The immunizing activity of either preparation (commercial Dick or specific toxin) was about equal, but with neither could 100% of older "positive" individuals be rendered negative.

At St. Paul's Orphanage a group of 50 children between the ages of 6 and 8 were given the 3 susceptibility tests. Of these, 31 reacted positively with both toxins. These 31 reactors were divided into 2 groups for immunization. The 1st group of 20 were given weekly intramuscular injections of 0.5 cc. of the specific toxin, in progressively increasing concentrations. When retested, 3 weeks after the 4th dose, 18 had become negative. The 2d group of 10 received each week 2 similar 0.5-cc. injections at a 1-hr. interval; 8 of these children were negative when tested 3 weeks after the 8th injection. That is, 87% of the 31 positive reactors became negative after 4 weekly injections of the specific toxin. When one compares the results of immunization in these 2 groups, viz., staff of Children's Hospital and younger children at St. Paul's Orphanage, differing widely in age, it is seen that nearly 30% more were rendered immune in the early age group than in the older.

With both the Dick and specific toxin, reactions of varying intensity were observed in practically all of the individuals immun-

ized. The majority of these reactions consisted of local soreness, with redness and more or less edema. Headache and nausea and in 3 individuals scarlatinoid rashes with rise of temperature and constitutional symptoms were also observed. These reactions might occur with different injections, although a few individuals reacted to every dose.

An attempt was made to immunize rabbits against both the specific toxin and nucleoprotein fractions and sheep and goat against the specific toxin. In only 1 of the 3 series of animals injected with nucleoprotein was an antiserum obtained. The 3 surviving animals yielded a potent antiserum which gave a positive precipitin test in dilutions up to 1 to 600. Besides the positive precipitin reaction, agglutination also could be obtained in a titer from 1 to 600 to 1 to 1200 against the 3 strains of Streptococcus scarlatinæ used, if the experiment was made with freshly drawn serum (15 to 20 hr.) or if guinea pig complement was added. Apparently sufficient complement was present in the fresh serum to suffice for the reaction. Positive agglutination was similarly obtained against all strains of Streptococcus pyogenes, including erysipelatis. On extending the observations to include streptococcus of various strains of the Holman classification, it was found that positive agglutination was also obtained with mitis, infrequens, equi, fecalis and equinus. With the following strains, viz., salivarius, anginosus, ignavus and non-hemolyticus, no agglutination was obtained. The differentiating feature between the 1st (positive) and 2d (negative) group is the ability of the former to ferment salicin. On this basis the streptococci can be divided into 2 divisions and hemolysis is not a differentiating characteristic. No agglutination was obtained with any of the pneumococci or members of the coli group. It is of interest to note that in the 2 rabbit series in which no antisera was produced, the injections were made during the winter months, as compared to the summer-injected series with positive sera. A more likely explanation for the negative results of immunization is the degradation and chemical change of the nucleoprotein taking place during incubation, especially if the latter be prolonged. Heidelberger and Kendall[6] have shown that several antigens are present in the acetic acid precipitable protein fraction. The various animals injected with the specific toxin readily developed an antibody, which gave precipitin reaction in fairly high titer with saline suspension of the specific toxin. However, similar precipitation phenomena were obtained when the antisera were used with a suspension of a precipitate obtained from uninoculated broth. It would appear that an immune body had been developed against the associated non-specific proteins derived from the media rather than against the specific toxin. Further proof of this assumption was observed in the complete lack of any neutralizing effect on the

toxin of the antisera. It should be borne in mind that the specific toxin is only a partially purified product. The fairly high solubility of the specific toxin in water (a property made use of in its concentration) also contributes to the difficulty in producing immune bodies.

Two interesting features developed by the work are the results of immunization. The 1st is associated with an antigenic nucleoprotein which gives a positive agglutination in the presence of complement with various strains of streptococcus characterized by the property of fermenting salicin. This nucleoprotein is closely allied to Heidelberger and Kendall's E, F and G fractions extracted from the Streptococcus scarlatinæ and also with Lancefield's[7] P nucleoprotein derived from Streptococcus hemolyticus. The low phosphorus content, together with high levorotation of our product would identify it more especially with Heidelberger and Kendall's F and G fractions, and implies, as these authors' work indicate, that a degree of hydrolysis had already taken place either during incubation or chemical manipulation (despite precautions against this) or both. Minor differences, such as decreasing percentage of phosphorus, in chemical composition of residues resulting from such degradations must necessarily occur. With a sufficient degree of hydrolysis there will ultimately result an end product devoid of any antigenic property. This we believe to be the explanation of our failure to obtain an agglutinating antiserum with the nucleoprotein in 2 of our 3 series. The strains of pneumococcus which were tested against our antisera were not studied for their fermentation of salicin as the relationship of the agglutinated strains of streptococcus to salicin was only discovered later. The importance of such cellular constituents to metabolism is seen by their relationship to fermentation.

The difference in the results obtained by immunization against the specific toxin in young and older individuals is probably more apparent than real. The fact that many nurses and physicians who persistently show a positive Dick reaction, yet despite continuous contact with scarlet fever, never develop the disease, argues strongly for their immunity. Furthermore, immunization procedures with the Dick series even when repeated fail to develop a negative reaction in these individuals and may even increase the extent of the positive skin reaction. Likewise a certain percentage of cases of scarlet fever are not followed by a negative Dick reaction. One is, therefore, forced to conclude that such individuals, even in the absence of a positive reaction with toxin boiled 1½ hr. (as is occasionally the case), are immune. We have found that altered conditions in the skin, chiefly allergic, may interfere with the Dick reaction to such an extent that the negative skin test is completely masked. Such pseudoreactions (the nature of which are at the

present under investigation and will be reported in a subsequent paper) are undoubtedly responsible for the apparent lack of immunity resulting from immunization procedures in older individuals.

Summary. Chemical and immunizing properties and the skin reactions of the nucleoprotein and specific toxin fractions separated from sterile filtrates of Streptococcus scarlatinæ have been studied and discussed.

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INCIDENCE OF SKIN DISEASES IN A STUDENT HEALTH SERVICE.

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Pollitzer[1] has given us a comparative statistical study of the incidence of skin conditions occurring among private and dispensary patients. More recently, Lane[2] published his compilation of dermatologic conditions taken from his experience in general practice, and Goodman[3,4] has undertaken a study embracing almost 1 million diagnoses representing both clinic and private practice. These figures include the findings of previous compilers in some instances, and may be considered as extremely accurate, due both to the large number of cases represented and the time period covered. There is an amazingly close correlation among the results of the different compilers despite the variation in the age and class of patient and the changes from time to time in diagnostic attitudes of the profession.

The present study, utilizing the figures and attendance at our recently organized health service, represents 1126 new diagnoses registered from January, 1932, to January, 1934. A tabular comparison of the results of Lane, Goodman and the present investigation. (Table 1, p. 269.)

The student group study was of an average age of 19, in good general health, and was composed of 90% men students and 10% women

students. The selection of cases covers 2 school years. As might be expected in this type of patient, tinea in some form was by far the most prevalent condition, with acne vulgaris second in occurrence. I believe with the present-day diagnostic conception and the further limitation of the diagnosis "eczema" that tinea is probably first in all tabulations and for this reason its importance is greatly enhanced. The high incidence of acne is a distinct reflection of the age of the group and the threshold of vanity.

TABLE 1.—TEN MOST COMMON SKIN CONDITIONS.

Guy Lane (Private General Practice).	Goodman (Clinic and Private Practice).	Gilman (Student Health).
1. Dermatitis	1. Eczema	1. Tinea
2. Eczema	2. Tinea	2. Acne vulgaris
3. Impetigo	3. Acne vulgaris	3. Seborrhea
4. Urticaria	4. Scabies	4. Verrucæ
5. Acne vulgaris	5. Psoriasis	5. Pyoderma
6. Herpes	6. Seborrhea	6. Dermatitis venenata
7. Verrucæ	7. Impetigo	7. Eczema
8. Tinea	8. Urticaria	8. Pityriasis rosea
9. Pruritus	9. Dermatitis venenata	9. Moles
10. Psoriasis	10. Alopecia	10. Herpes zoster

In the diagnosis of tinea (or ringworm) included, of course, are fungus infections of the toes, hands and groin (not necessarily laboratorily confirmed), ringworm of the body, tinea versicolor (of which there were surprisingly few), plantar warts, ringworm of the nails and dyshidrosis. In this group, ringworm of the feet, hands and groin constituted $\frac{2}{3}$ of the cases.

The diagnosis of acne vulgaris was given for the classical picture of this condition, ranging from mildly seborrheic skins with many comedones to the completed ensemble with fully developed pustules. This is probably less than the actual incidence, as I am convinced that fully $\frac{1}{2}$ of the student population has some form of acne vulgaris.

Seborrhea includes in this compilation the usual well-defined seborrhea of the skin and scalp, seborrheic dermatitis and the early seborrheic alopecias of students. This latter condition, apparently on the increase in young men students, accounts for the relatively prominent position of seborrhea in the present tabulation. Verrucæ appear high up in the list, due to the students' willingness to avail themselves of the cosmetic aid furnished by the health service.

Pyoderma is a convenient term for almost all simple forms of pyogenic dermatitis which includes "impetigo," mild sycoses, secondary infections and furuncles. Pyoderma (impetigo) occurs in all 3 groups as well as in Tauber's[5] list of common skin conditions in children.

Dermatitis venenata, by which is meant acute or subacute dermatitis due to some external irritant, *i. e.*, rhus tox., although among the 10 commonest conditions, represents only 4% of the new diagnoses. In this connection I might add that chronic dermatitis

of external origin has been included among the eczemas. Were we to limit ourselves to the true diathetic eczema of adolescents and young adults (Besnier, Rost), the diagnosis of eczema would not appear in our tabulation. However, conforming to the larger concept of eczema maintained by European and some American dermatologists, I have included certain chronic dermatoses of internal and external origin as well as certain cases of circumscribed chronic patchy dermatitis and *neurodermite*.

Pityriasis rosea occurred often enough to include it in the list of 10, and under circumstances highly suggestive of mild contagion. This, too, does not represent the total number of cases, as some were undoubtedly seen in other departments of the service. Moles may be considered in the same light as warts, *i. e.*, the availability of operative relief called forth a high percentage of response. Herpes zoster occurred mainly in a mild and practically painless or asymptomatic form. No association with varicella was noted; in fact, no case of the latter has been seen during the period under study. If one were to exclude both warts and moles from the tabulation, then molluscum contagiosum and herpes simplex would be No. 9 and No. 10 in the list.

It is striking that scabies, pediculosis and psoriasis, although common in Lane's and Goodman's lists, do not appear here. Seven cases of each were seen during the 2-year period. Quite likely the majority of simple parasitic infections were self-diagnosed and self-treated. The scarcity of scabies is striking—and we may expect an "epidemic" at any time. Urticaria was an uncommon symptom-complex in the medical as well as the dermatologic department. The remaining skin conditions usually regarded as of fairly common occurrence were seldom seen due to the limitations of the age of the student group.

The present tabulation is similar to those previously reported and particularly to that of Lane representing a cross-section of general practice. It bears out the contention of Goodman and others that, since 10 skin conditions constitute from 60 to 78% of those seen in practice, they at least deserve that proportionate amount of study and attention by the student and the practitioner.

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GONOCOCCEMIA WITH RECOVERY.

REPORT OF FOUR CASES.

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THERE is abundant evidence that arthritis, tenosynovitis and other commonly observed benign gonorrheal complications result from the invasion of the blood stream by gonococci. Nevertheless, published observations reveal that only rarely are gonococci isolated from the blood in such instances. Recently Filler[1] reported the 7th case of gonococcemia recovering without a persisting cardiac lesion. The case of Thayer[2] and possibly also that of Tapie and Riser[3] should be added to these. In addition there have been several instances of gonococcemia and endocarditis recovering with a valvular deformity. (Silvestrini,[4] Dieulafoy,[5] Marfan and Debré,[6] Withington,[7] Perry,[8] Newman.[9])

In view of the paucity of such reported cases, it seems of value to report 4 recovered cases of gonococcemia (positive blood cultures) occurring in this hospital within the last 2 years. Three of the patients are perfectly well; the fourth, reported in detail by Newman,[9] developed a cardiac lesion.

Wheeler and Cornell[10] and Garlock[11] have each reported a case of gonococcemia in which they ascribed recovery to removal of a focus of infection. They believed they had eradicated the original source of the bacteremia by uterine curettage and salpingectomy. In view of these reports it is worthy of note that all of our recoveries occurred under conservative therapy and without any radical method of treating the source of the infection.

Case Reports. CASE 1.—D. K., white (admitted August 1, 1931; discharged September 19, 1931), a 33-year-old waitress, was well until 2 weeks before admission when she developed a sore throat associated with slight cough, nasal congestion and supraorbital pain. Two days later she awoke with severe abdominal pain localized to the left lower quadrant, associated with a temperature of 104° F.

There was nasal congestion and injection of the pharyngeal mucosa. There was moderate tenderness and resistance in the lower abdomen. Pelvic examination revealed a soft, tender, fluctuating mass behind the uterus. The blood pressure was 102/68; hemoglobin, 70%; blood leukocytes, 17,000 (polymorphonuclears, 90%; lymphocytes, 8; monocytes, 2); sedimentation time, 5 minutes. Urethral and cervical smears were negative for gonococci. The blood Wassermann test was negative. Temperature, 103.4° F.; pulse, 120.

A diagnosis of pelvic abscess was made. A posterior colpotomy was performed and 23 ounces of odorless, yellow, creamy pus was obtained which was sterile on culture in routine media. Five days after operation the patient developed joint pains involving the fingers and left elbow. The

joints were moderately swollen, red and extremely tender. The patient had a chill; her temperature rose to 104° F. and her pulse to 146 per minute. A blood culture taken at this time was reported as containing gonococci. On the 13th postoperative day she developed an acute arthritis of the left sternoclavicular joint. There was a faint blowing systolic murmur at the apex of the heart, which later disappeared. The edge of the spleen was palpable. A second blood culture, taken when the temperature was approaching normal, and a blood complement-fixation test were both reported negative. After 3 weeks, patient's temperature was normal, her joint symptoms gradually subsided on treatment with wet dressings, and she was referred back to her physician for physiotherapy. The patient has now been followed for 2 years, and except for chronic pelvic inflammatory disease is well.

CASE 2.—I. S., white (admitted February 20, 1932; discharged March 27, 1932), a 30-year-old housewife, developed swollen red, painful joints, particularly the left knee and right wrist, 1 month before admission. During this period she had intermittent fever up to 102° F., occasional chills, and vomiting. On the day before admission she developed a rash on the arms, legs, hands and feet. The lesions were heralded by a drawing sensation at the site of the lesion, then redness appeared followed by a blackish discoloration and vesicle formation. On the same day she claims to have had about 10 chills.

The temperature was 103° F.; pulse, 114. The patient appeared acutely ill. In the skin of both upper and lower extremities there were numerous pink and purplish papules, singly and in groups. The older lesions appeared bluish-black with superimposed bullæ or pustules. Some of these were dry and covered with crusts. A few lesions were situated on the palmar aspect of the hands and the plantar aspect of the feet. The right wrist, hand and fingers were the site of an inflammatory process. The fingers were abnormally warm, somewhat edematous and tender. The function was almost completely inhibited due to the extreme pain on motion of the affected joints. Over the left elbow there was fullness, warmth and tenderness, and pain on motion. Aside from the presence of a soft, blowing systolic murmur over the apical region of the heart, the remainder of the physical examination revealed no abnormality. The blood pressure was 113/73. The hemoglobin was 63%; erythrocytes, 4,200,000; leukocytes, 16,500 (80% polymorphonuclears, 13 lymphocytes, 4 monocytes, 2 eosinophils). The contents of the bullæ were of serous nature and free from organisms on smear.

The diagnosis was acute general infection (sepsis), infectious arthritis, probably gonorrheal. The skin lesions were interpreted as erythema multiforme, probably of septic origin.

The temperature ranged between 101° to 104° F. for 2 weeks, and then gradually returned to normal. The urine was normal, as was a Roentgen ray of the chest. No focus of infection could be found in the pelvis. The arthritis yielded gradually to treatment by wet dressings and immobilization. Smear of the fluid from the left elbow joint revealed neutrophils containing Gram-negative diplococci. The patient's husband admitted having intercourse with her while he had a subacute gonorrheal urethritis 3 months before hospitalization. A gonococcus was grown from the blood stream but only in the fluid media. The blood Wassermann and gonococcus complement-fixation tests were negative. Roentgen ray of the right wrist showed absorption of the bone at the intercarpal joint. The heart was normal on Roentgen ray and the systolic murmur disappeared. The electrocardiogram showed only an inversion of T in Lead III. With rest in bed, sedatives and the application of a rubber bandage (Bier hyperemia), the joints improved markedly. She was given a course of gonococcus vaccine intramuscularly, following which she was discharged considerably better, afebrile, and showing only some immobility of her joints. Follow-up after a year shows her completely well.

CASE 3.—I. D., white (admitted August 28, 1933; discharged October 8, 1933), a 23-year-old police constable, contracted gonorrheal urethritis 4 months before admission. Two weeks before admission he developed severe pain in the right shoulder and right calf, and generalized aches and pains. The next day he suffered pain in the right forearm and left thumb. Ten days before admission he developed severe pain and slight swelling of the joints of the right foot followed by similar symptoms in the left. At the same time there was a papular eruption with inflammation of the fourth toe of the right foot, and a large area of erythema on the dorsum of that foot. His physician made a diagnosis of gonorrheal arthritis and he was treated by bed rest and hot applications to the affected joints. While the joint pains diminished he suffered marked sweats, fever between 100° to 103° F., and was unable to walk because of pain. On the day of admission he developed swelling of the wrist and a small erythematous area on its dorsal aspect.

The patient appeared acutely ill. His temperature was 104.4° F., his pulse 120 per minute. There were scattered round areas of erythema on the left wrist, left shoulder, right side of neck and chest, thighs and feet. There was a large erythematous area over the dorsum of each foot. Both feet were moderately swollen and hot. There was distinct tenderness over the dorsum of both feet, and pain was referred to this same region on pressure or by moving the toes. A systolic murmur was heard over the apex of the heart; otherwise the examination revealed nothing abnormal. The blood pressure was 126/80. The leukocytes numbered 30,000 (neutrophils 86%, lymphocytes 9, monocytes 5). The sedimentation time was 36 minutes. The urine was normal.

The diagnosis was gonococcemia, gonorrheal arthritis. On the day following admission the cutaneous lesions became more numerous, and in several places assumed a hemorrhagic pustular or vesicular character, making the diagnosis of gonococcemia more probable as similar lesions had been observed in other cases of gonococcal infection. Fluid obtained from one of the skin lesions contained polymorphonuclear leukocytes but no organisms. A tenosynovitis of the right foot developed, but fluid from this region showed no gonococci. The gonococcus complement-fixation test was negative. Blood culture revealed gonococci on all of the fluid media. Fever lasted 2 weeks and then subsided. The joints were treated by wet dressings and gradually improved. The patient also received gonococcus vaccine intramuscularly.[8] After 6 weeks he was able to walk around with only slight pain, which was relieved by arch supports. The sedimentation time was over 2 hours, and patient was discharged to receive physiotherapy.

CASE 4.*—E. S., white (admitted January 15, 1932; discharged February 27, 1932), a 19-year-old, unmarried girl, had a 4 months' pregnancy terminated by vaginal tamponage 3 months before admission. The next day she developed severe abdominal pain in the right lower quadrant associated with fever of 104° F. One week later a curettage was performed, following which she had daily chills with fever rising to 105° F. In addition there were profuse night sweats and progressive anemia requiring a transfusion.

The patient was an undernourished, pale woman, with petechiæ in the right lower conjunctiva and clubbing of fingers. The heart was slightly enlarged to the left, and a short systolic murmur was heard at the apex and a blowing diastolic murmur to the left of the sternum in the fourth interspace. The spleen was felt two fingers below the costal margin. Pelvic examination revealed a slightly patulous eroded cervix with a grumous discharge, thickened adnexæ, and a retroverted and retroflexed uterus. The temperature was 101.8° F. and the pulse 128 per minute. The urine contained albumin, 2 to 5 erythrocytes per high-power field, numerous leukocytes, and occasional hyaline and granular casts. The

* This case was reported in detail by Newman.[9]

hemoglobin was 62%; erythrocytes, 4,550,000; leukocytes, 5480 (83% neutrophils, 17% lymphocytes). Blood pressure, 108/70. Sedimentation time, 40 min. Cervical smear was negative for gonococci. Blood Wassermann test, negative.

The diagnosis was chronic sepsis (postabortion); pelvic thrombophlebitis.

The patient continued to run a septic course with frequent chills and temperature spiking between 94° and 103° F., and occasionally higher. She was given a transfusion for increasing anemia. Fluoroscopy of the heart suggested aortic insufficiency with a mitral lesion. (There was no history of rheumatism or cardiac ailment preceding the present illness.) A diagnosis of subacute bacterial endocarditis was entertained. Two blood cultures were reported as positive for gonococci. A third and fourth culture were both negative. Gonococcal complement-fixation test was reported 4+ 4 days after admission, 2+ just before discharge. After 3 weeks the temperature returned to normal, spleen receded and urine became normal. Follow-up after 1 year revealed that the patient was symptom-free, married and 5 months pregnant. The blood pressure was 124/68. Cardiac examination showed the presence of a systolic murmur over the apex and a low-pitched diastolic murmur to the left of the sternum.

Diagnosis. The essential features of these cases, as well as of those previously reported, may be gleaned from Table 1. Certain points deserve special comment. As a rule arthritis is present with the onset of gonococcemia. A general gonococcal infection may be present, however, without a simultaneous arthritis. Where, as in our third case and that of Thayer,[2] no arthritis was present, the diagnosis becomes more difficult. Sometimes the primary infection is already healed and no organisms are found in the genital tract. In such cases the history or recovery of the organism from a metastatic focus (elbow, Case 2) will establish the nature of the primary disease. Blood stream infection is suspected from the general constitutional symptoms, absent in uncomplicated gonococcal urethritis, arthritis or salpingitis. The patients are more acutely ill than a local infection would warrant. Almost invariably patients have chills and high fever, generally of intermittent or remittent character, sweats, anemia, leukocytosis, increased sedimentation rate.

Of special significance are the skin lesions which are almost invariably present. These in themselves are probably not specific for gonococcemia, but in conjunction with other evidences of gonorrheal infection are highly suggestive of a general infection. The lesions occur on the extremities, the trunk and occasionally the neck; the face is spared. They appear as crops of macules or papules, sometimes of hemorrhagic nature. They disappear in 2 or 3 days and may recur. More suggestive are the vesicular or pustular lesions found in Cases 2 and 3 and likewise reported by Jenkins,[12] Cabot,[13] O'Brien and Bancker,[14] and by Filler.[1] Unlike the cutaneous lesions in other general infections, these contain no organisms. The association of a recent or active gonorrheal urethritis or arthritis with cutaneous lesions in a patient who appears acutely ill should lead to a diagnosis of gonococcemia. On this basis, the diagnosis was made on admission in our most recent case (Case 3) before blood cultures were taken.

TABLE I.—SUMMARY OF ESSENTIAL CLINICAL FEATURES OF RECOVERED CASES OF GONOCOCCEMIA.

Author.	Age and sex.	General appearance.	Temperature.	Chills.	Arthritis.	Cardiac murmurs.	Cutaneous lesions.		Gonococci in genital tract.	Embolic phenomena.
							Maculopapular eruption.	Pustules.		
Thayer[2]	28 ♂	....	99–104	+	..	Systolic	+ abdomen	....	+	0
Jenkins[12]	38 ♂	Toxic, prostrated	102–104	+	+	...	+ in crops on extremities	+ hand	+	0
Cabot[13]	26 ♀	....	98–103	+	±	...	0	+ thumb, wrist	+	0
O'Brien and Bancker[14]	21 ♂	Acutely ill	To 104	+	+	Systolic	0	+ neck, arm, legs	+	0
Wheeler and Cornell[10]	19 ♀	Acutely ill	....	..	+	Systolic	+ (with purpura) generalized	0	+	0
Garlock[11]	26 ♀	Acutely ill	To 104	..	..	Systolic (apex) Sys.-Dias. (base) (transient)	+ trunk, extremities	0	+	0
Rubenstone and Israel[15]	21 ♀	....	102–103	+	+	Systolic	+ trunk, extremities	0	+	0
Filler[1]	31 ♀	Acutely ill	....	+	+	Systolic	+	+ lower extrem.	+	0
Friedberg (Case 1)	33 ♀	....	100–104	+	+	Systolic	0	0	0	0
Friedberg (Case 2)	30 ♀	Acutely ill	101–104	+	+	Systolic	+	+	0 (positive from elbow)	0
Friedberg (Case 3)	23 ♂	Acutely ill	100–104	+	+	Systolic	+	+	0	0
Newman[9] (Friedberg, Case 4)	19 ♀	Chronically ill	96–104	+	0	Systolic Diastolic	....	....	+	+

Once this diagnosis or indeed the presence of any general infection is suspected, blood cultures should be made until the diagnosis is confirmed or discarded. Owing to the fact that the gonococcus is a difficult organism to grow, one or two negative blood cultures cannot eliminate the possibility of a gonococcemia. Since chills and high fever are so frequent in this disease, the most opportune time for blood culture is during or just after such an episode. In 2 of our cases the only positive cultures were obtained after chills followed by fever up to 104° F. Cabot[13] and Rubenstone and Israel[15] specifically mention that their positive cultures were obtained after chills. If no chills are observed, positive results will be obtained most frequently if blood cultures are taken immediately after the temperature has reached a high point, provided this attains approximately 104° F. All of our negative cultures were obtained when these were taken at temperatures below 103° F. It appears that positive blood cultures may be obtained more frequently in cases of gonococcal infection if the presence of a gonococcemia is suspected, if blood cultures are made more opportunely, and if suitable methods for the cultivation of the gonococcus are employed.

The blood culture technique presently employed at the Mount Sinai Hospital laboratories was described by Crohn and Shwartzman,[16] Lichtman and Gross,[17] and by the writer.[18] The important features are the comparatively large quantity of blood withdrawn (21 cc.), the use of both fluid and solid media, and of a variety of media differently enriched in order to favor any organism that may be encountered. The routine procedure in these laboratories is to observe the culture media for at least a week before reporting them as sterile. Rarely do gonococci appear before the fourth day. Where a gonococcemia is suspected, the original fluid cultures are subcultured on ascitic agar even when the smear of the original culture is negative. Since organisms grow on the solid media in the original cultures only when they are present in large numbers, it is probable that in none of our patients were the gonococci abundant in the blood stream as they grew only in the fluid media.

Bacteriologic Technique. The presence of gonococci in the blood culture media was verified in the following manner: When smears revealed Gram-negative diplococci with the characteristic morphology of the Neisserian organisms, subcultures were made onto several media as follows: (1) 1% ascitic-glucose agar (plates and slants); (2) blood agar plates; (3) liver hormone ascitic-fluid 1% agar of pH 6.8 and 7.6 (a local modification of Huntoon's beef-heart hormone); (4) plain agar. The media were moist and warm before inoculation of the cultures.

When colonies with a morphology suspicious of gonococci (see below) appeared, generally between 48 and 96 hr., on the liver hormone or ascitic fluid media or both and failed to grow on the plain agar, these colonies were subcultured again on the most favorable media for final identification. Such identification depended upon satisfaction of the final criteria: (1) Failure to grow on plain agar media; (2) poor growth on the blood agar plates; (3) good growth on ascitic-fluid or liver hormone ascitic-fluid agar; (4) characteristic morphology of the gonococci, namely, a delicate growth

of grayish-white, translucent, very finely granular colonies resembling dewdrops which, on smear stained by Gram's method, revealed Gram-negative coffee-bean shaped diplococci; (5) positive agglutination test. The serum for agglutination was a polyvalent gonococcal serum prepared by Lederle. A light suspension of the organisms was employed. Tubes were incubated for 24 hr. at 37° C. Controls of agglutination were run with polyvalent New York Board of Health antimeningococcus serum. A positive result consisted in agglutination of the gonococci up to 1 to 320 with a lower or equal (but not higher) agglutination titer with the antimeningococcus serum.

Wheeler and Cornell[10] have distinguished two types of cases of gonococcemia; those which have consistently positive and those with intermittently positive blood cultures. The former are said to occur in patients with endocarditis and indicate the more serious prognosis. In our experience, blood cultures have been equally intermittent in those cases that recovered and those that resulted fatally because of a gonococcal endocarditis. We believe the time and method of making the blood culture are more significant in determining the bacteriologic findings in gonococcemia than the added presence of endocarditis.

Having established the presence of gonococcal bacteremia, I believe we can predict the outcome with a high degree of accuracy. Thayer[19] and others have shown that those patients with a general infection due to the gonococcus, who succumb, almost invariably have a complicating gonococcal endocarditis. The prognosis therefore depends upon the presence or absence of endocarditis. This can be determined on clinical features alone, without consideration of bacteriologic findings. While, in general, blood cultures may be obtained more consistently in cases with endocarditis, even in these the bacteremia is essentially an intermittent one and, as we have mentioned, positive blood cultures occurred irregularly even in our fatal cases with endocarditis.

According to generally accepted studies, fever, chills, anemia and other constitutional reactions are present in general infections whether a patient has endocarditis or not. The other symptoms, which may be termed specific ones, are definitely referable to endocardial involvement. These specific symptoms consist essentially of embolic phenomena and alterations in heart sounds.[20] Under embolic phenomena, we do not include the cutaneous lesions already mentioned, since these lesions are free from organisms and their origin is not necessarily from vegetations on the heart valves. White centered petechiæ, when present, are very suggestive of bacterial endocarditis, but they may occur in other conditions. More significant is the occurrence of embolization with infarction of various organs. Embolization is revealed by occlusion of an artery of an extremity, by hematuria and other renal symptoms, hemoptysis and chest pain (due to pulmonary infarction), sudden sharp pain in the left hypochondrium or shoulder (splenic infarction and perisplenitis), and occasionally hemiplegias. Some of these symptoms are, of course, not conclusive of embolization. More direct evidence of endocarditis is found in the sudden development

and alteration of murmurs. A glance at Table 1 will indicate that a transitory systolic murmur is a frequent occurrence in gonococcemia even in recovered cases without endocarditis. For this reason, significance can be attached only to diastolic murmurs, not previously present, which develop in the course of the bacteremia and which remain persistently. Such occurrence in the course of gonococcemia is highly suggestive of the presence of bacterial vegetations on the heart valves. Case 4 in my series developed such a murmur, as well as white centered petechiæ and evidence of nephritis. While this case and a few other similar recoveries with endocarditis have been reported, the diagnosis of gonococcic endocarditis should lead generally to a hopeless prognosis. Conversely the absence of symptoms of endocarditis points almost invariably to a favorable prognosis.

Summary. 1. Four cases of gonococcemia are reported in whom recovery occurred under conservative therapy.

2. Careful clinical observation and the employment of adequate blood culture technique may lead to the more frequent diagnosis of this condition.

3. In the cases thus far reported, recovery generally occurred if there was no complicating gonococcal endocarditis. The latter is recognized by the presence of embolic phenomena and the development of persistent diastolic murmurs.

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Erratum.

In the July issue of the American Journal of the Medical Sciences, on Page 91, Line 4, the sentence should read, "The spleen was examined for kerasin by Dr. John G. Reinhold and was found to contain that substance in the proportion of 6.02% of the dried spleen."

BOOK REVIEWS AND NOTICES.

ALLERGY IN GENERAL PRACTICE. By SAMUEL M. FEINBERG, M.D., F.A.C.P., Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School; Professor of Medicine in the Cook County Graduate School of Medicine; Attending Physician, Cook County Hospital, Chicago. Pp. 339; 23 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1934. Price, $4.50.

PROBABLY 1 person in every 7 is hypersensitive to some foreign substance and is, therefore, a potential sufferer from one or more of the many clinical manifestations of allergy. The problem of diagnosis and management, therefore, occurs very frequently in the experience of the physician. To afford the practitioner an opportunity to inform himself on the subject, the author set himself the task of preparing a text sufficient for practical purposes, and yet not as exhaustive as the existing complete works for special students in the field. He has on the whole achieved his objective fairly well, in spite of the pardonable tendency of the enthusiast at times to go unnecessarily into detail, and a certain prolixity of style. The practitioner will find the book useful and instructive. R. K.

PHARMACOLOGY AND THERAPEUTICS. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Tenth edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., Professor of Pharmacology in the University of Oxford, Oxford, England. Pp. 786; 75 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $6.50.

THE classic textbook in its field, this "first severely critical rigorously scientific general text-book to be written in English by an experimental pharmacologist" has maintained its popularity for a third of a century. This, the second edition to be published since Cushny's death, contains a biographical note, "lest an oncoming generation . . . . may forget that the Man was greater than the Book." The appearance of the British Pharmacopœia of 1932 has required extensive revisions. The growth of constructive pharmacology is recognized by the inclusion of extensive additions, though many omissions indicate the continuing importance of its destructive and critical function. E. K.

HYPERTENSION AND NEPHRITIS. By ARTHUR M. FISHBERG, Associate Professor to Beth Israel Hospital; Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 668; 39 illustrations and 1 colored plate. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $6.50.

THIS new volume of a standard work has been extensively revised. The general arrangement of the subject matter is logical and well presented, the style is readable, and the illustrations are well chosen. The book can warmly be recommended as a thoroughly reliable and modern guide to a group of common and important diseases. B. L.

OBSTETRIC MEDICINE. Edited by FRED L. ADAIR, M.A., M.D., F.A.C.S., Mary Campau Ryerson Professor of Obstetrics and Gynecology, etc., and EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago, etc. Pp. 743; 24 illustrations and 2 colored plates. Lea & Febiger: Philadelphia, 1934. Price, $8.00.

THIS volume, edited by an obstetrician and an internist, brings before us the views of a group of 39 distinguished contributors regarding the relation of pregnancy to the commoner diseases which may appear as complications, or in which the pregnancy may be an intercurrent happening. The 12 sections include not only a discussion of medical conditions but also associated diseases of the eye and the skin, and disorders of body mechanics.

The first section considers physiology of pregnancy, physical diagnosis as influenced by pregnancy, and pharmacology as limited by pregnancy. Under the title Fetal Disorders, the relationship of heredity and intrauterine development to subsequent events is brought out, with a discussion of the laws of eugenics and euthenics. The text proceeds through such infectious diseases as tuberculosis and the venereal diseases, and the contagious tropical and parasitic diseases. Following this are excellent discussions of avitaminoses, the lesions of the nervous system, disorders of the respiratory tract, the diagnosis and management of heart disease, and diseases of the arteries.

In the section on disorders of the alimentary tract, well considered discussion of dental lesions and an able section on appendicitis during pregnancy. The chapter on diseases of the kidneys includes a new and logical classification of nephritis in pregnancy with details of the most dependable function tests. Illustrative case histories add much to the discussion of this section. The surgical conditions of the urological tract are fully discussed.

In the important section on disorders of the endocrine balance, the authors stress the thyroid and ovary, constitutional types and diabetes mellitus. The section on disorders of the blood is a very complete recapitulation of the blood dyscrasias in relation to pregnancy; methods of blood study are detailed with explanations of findings. Therapy is fully considered. The final sections deal with the diseases of the skin, orthopedic complications and herniations.

In this unusual book the specialist in either medicine or obstetrics will find much of value in the thorough manner in which the subjects have been handled. Such a coördination of diagnosis and treatment of various pathologic states complicating a normal physiologic process should be of extreme value to the general practitioner who may not have available consultants in many various branches. P. W.

CHRONIC NASAL SINUSITIS AND ITS RELATION TO GENERAL MEDICINE. By PATRICK WATSON-WILLIAMS, M.D., Hon. Consulting Surgeon in Diseases of the Ear, Nose and Throat, Bristol Royal Infirmary, etc. With a Foreword by SIR HUMPHREY DAVY ROLLESTON, BART., G.C.V.O., K.C.B., Physician Extraordinary to H. M. the King; Emeritus Regius Professor of Physics, Cambridge. Pp. 262; 123 illustrations. Second edition. Baltimore: William Wood & Co., 1933. Price, $5.00.

ALTHOUGH this volume has as its purpose the elaboration of the author's exploral-suction technique in the diagnosis of nasal sinusitis, an attempt is also made to trace the processes of focal sepsis and to outline the systemic effects of nasal sinus infections. The account of the pathogenesis of the systemic toxemias and secondary infections due to chronic nasal sinusitis will interest the student of general medicine quite as much as the rhinolo-

gist. Numerous clinical examples, interspersed throughout the monograph, clarify the arguments and will hold the attention of the practical clinician. Reiteration of exploral-suction technique seems highly desirable in view of the practicability of evaluating the status of every sinus and obtaining adequate cytologic study. The section on endorhinoscopy will offer little to rhinologists in this country, where the procedure has been generally employed for some time, but will offer the beginner an excellent expose of the utility of this instrument. A position of conservatism is maintained in regard to sinus surgery, and the conclusions concerning the efficiency and preferability of pernasal operations seem justified. The use of photomicrographs and plates prepared from anatomical material enhances the text. The volume will prove stimulating reading to the rhinologist mainly because the author has a somewhat fresh view of the commonplaces of rhinology. H. S.

A System of Clinical Medicine. By Thomas Dixon Savill, M.D. (Lond.). Edited by Agnes Savill, M.D., assisted by E. C. Warner, M.D. Pp. 1063; 162 illustrations. Ninth edition. Baltimore: William Wood & Co., 1933. Price, $9.00.

This book differs from other textbooks of medicine in the manner of its approach to the subject. Instead of a series of descriptions of disease pictures, the presentation is from the standpoint of what the physician finds at the bedside, *e. g.*, acute abdominal pain; its possible causes. That the work has reached its 9th edition is ample proof of its popularity and usefulness. Seventeen authors have contributed to the volume.

R. K.

Red Medicine: Socalized Health in Soviet Russia. By Sir Arthur Newsholme, K.C.B., M.D., formerly Principal Medical Officer of the Local Government Board of England and Wales, and John Adams Kingsbury, LL.D., Secretary of the Milbank Memorial Fund, formerly Commissioner of Public Charities, City of New York. Pp. 324; illustrated. Garden City, N. Y.: Doubleday, Doran & Co., Inc., 1933. Price, $2.50.

An extremely interesting description of what Soviet medical practice aspires to be, and, more especially, what it would like the rest of the world to believe that it now is. For the material here presented is what the authors (neither of whom speaks Russian) were shown, or told, in the course of their Russian tour which lasted a month and was in considerable part spent in travelling 9000 miles. The reader should bear this in mind lest he be misled into unwarranted conclusions by a presentation that is very well and plausibly made. In any event, all readers, medical and lay, will find here much food for thought. R. K.

Essentials of Medical Electricity. By Elkin P. Cumberbatch, M.A., B.M. (Oxon.), D.M.R.E. (Camb.), M.R.C.P., Medical Officer in Charge, Electrical Department, and Lecturer on Medical Electricity, St. Bartholomew's Hospital, etc. Pp. 508; 132 illustrations and 15 plates. Seventh edition revised and enlarged. London: Henry Kimpton, 1933. Price, 10/6.

This edition, clearly describing the fundamental theoretical and practical applications of medical electricity, should be a valuable reference to teachers of physics, especially in courses designed for pre-medical students. The

different electrical circuits are well illustrated by diagrams followed by pictures of different types of electrical apparatus.

The former chapter on high frequency and diathermy has been expanded to 7 chapters. No mention is made of the "inductotherm," a new electrical apparatus for producing artificial fever without electrodes. The practical application of different electrical circuits in various forms of treatment is developed in detail with frequent illustrations. The illustrations of the motor points of the muscles of the body should be useful in the application of electrical currents. J. W.

THE LYOPHILIC COLLOIDS. (THEIR THEORY AND PRACTICE.) By MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati, and MARIAN O. HOOKER, Research Associate in Physiology in the University of Cincinnati. Pp. 246; 84 illustrations. Springfield, Ill.: Charles C Thomas, 1933. Price, $4.50.

THE writers have for many years been engaged in the study of colloidal phenomena and their application to living matter. They discuss the general nature of lyophilic colloids, chemical application, and biological application. It is the aim of the work to explain "why biologists have not been able to rediscover, in living matter, the laws particularly of the physical chemists; and also why another point of view is due in chemistry if we would understand a host of problems of the existence of which, but not the solution of which, the workers in pure or applied chemistry have long been cognizant." It is only fair to point out that much of the matter discussed is controversial. Some of the authors' views are not generally shared. This is precisely the reason why the interested reader will find it of profit to have the work of Fischer and Hooker so conveniently presented in book form.

B. L.

PHYSICAL CHEMISTRY OF LIVING TISSUES AND LIFE PROCESSES. AS STUDIED BY ARTIFICIAL IMITATION AT THEIR SINGLE PHASES. By R. BEUTNER, M.D., PH.D., Professor of Pharmacology, School of Medicine, University of Louisville. Pp. 337; 79 illustrations. Baltimore: The Williams & Wilkins Company, 1933. Price, $5.00.

THE object of this work is expressed in the subtitle. The author has collected the very extensive literature that bears on the artificial imitation of life processes. There are discussed artificial models which reproduce certain phenomena peculiar to living organisms; the physical laws of such models; and the application of these laws to biological problems. The work is divided into several sections: Life as a scientific problem; membranes, osmosis and related forces; life processes related to crystallization or due to surface force; electrical currents in tissues and their relation to life processes; the outlook to future possibilities. It is no sense a textbook, but rather a reference work and one which will stimulate thought and the imagination. B. L.

BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY. By DAVID H. BERGEY, Formerly of the University of Pennsylvania, Philadelphia. Assisted by a Committee of the Society of American Bacteriologists. With an Index by ROBERT S. BREED, New York Agricultural Experiment Station. Pp. 664. Fourth edition. Baltimore: The Williams & Wilkins Company, 1934. Price, $6.00.

THE fourth edition in 12 years, this includes the advances made since 1930. Two new genera have been recognized—Brucella and Listerella, and

Pfeifferella and Actinobacillus have been combined. Fifty new species are included and several omitted, as synonymous with other species. With 100 pages added, this new edition would seem indispensable to bacteriologic laboratories. E. K.

DIET IN SINUS INFECTIONS AND COLDS. By EGON V. ULLMAN, M.D., Formerly Special Lecturer for Biology at the Oregon State College; Instructor at the First Medical Clinic at the University of Vienna, etc. Recipes and Menus by Eliza Mez. Pp. 166. New York: The Macmillan Company, 1933. Price, $2.00.

DENYING the major rôle of an infectious agent, the author propounds the view that dietetic error is the essential cause of colds. (Yet in the title he speaks of sinus *infections!*) Cure and prevention by salt-low, alkaline, fruit-juice, vegetable-juice, back-to-nature diets are preached with the usual fervor—and paucity of proof—of the diet enthusiast. R. K.

CHINESE MEDICINE. By WILLIAM R. MORSE, M.D., LL.D., F.A.C.S. Vol. XI of Clio Medica. Pp. 185; 20 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $2.50.

THIS is more than a history of Chinese medicine; it is also a sympathetic and informing account of Chinese philosophy, perhaps the most grotesque and most difficult to comprehend of any of the world's philosophies. Starting in the remote past with a dualistic conception of the universe, China's philosophy has developed in a maze of involved abstract speculation utterly foreign to the Western mind which has its roots in the sane and critical philosophy of the Greeks. The peculiar type of intensive speculation in which the Chinese have indulged for nearly three millenia has undoubtedly retarded the Chinese in a material direction. On the other hand, it has produced a peculiarly high moral dignity that has impressed all foreigners who have come in contact with educated Chinamen. Two different persons, one a medical missionary, one a novelist, told the Reviewer that in the presence of high-bred Chinese they experienced a distinct and uncomfortable sense of racial inferiority, a feeling that no European or American had ever given them.

The book deals interestingly with Chinese anatomy, physiology, diagnosis, based almost exclusively on the pulse, with materia medica, with the practice of medicine and surgery. The drugs used by the Chinese are like those employed in Europe during the Middle Ages; a few, such as Ma Huang (ephedrin), have definite value.

It has been claimed by the Chinese that they discovered the circulation of the blood over 2000 years before Harvey, but the statement probably represents nothing more than a poetic figure of speech. A number of characteristic illustrations and a long bibliography enhance the value of this interesting addition to Clio Medica. D. R.

ATLAS OF PATHOLOGICAL ANATOMY, VOL. 1. Compiled by E. K. MARTIN, M.S., F.R.C.S. Pp. 489, mostly illustrations, many colored. Baltimore: William Wood & Co., 1933. Price, $15.00.

THIS first volume of the Atlas of Pathological Anatomy comprises the drawings of pathological specimens which have appeared as a supplement to the British Journal of Surgery during the years 1926 to 1930.

As the title indicates, the main feature of the book lies in the illustrations, which have been drawn from surgical specimens removed at operation

as well as autopsy material. The specimens have been selected from the Hunterian Museum of the Royal College of Surgeons and several of the better known British university medical museums. This first volume treats of tumors and inflammations of bone, and diseases of the stomach, breast, kidney, gall bladder and bile ducts.

The usual tendency in works of this type is to lay too much stress on the rare and the unusual and it is to the credit of the author that he has included only typical examples of the more common lesions, a fact which, especially for teaching purposes, greatly enhances the value of the book.

There are over 250 plates in the book, of which about half are in color. The majority are of gross specimens, the remainder showing typical microscopic fields. The color plates are unusually well done and give an excellent idea of the tissues as they appeared during life. The specimens illustrated indicate careful selection from a wealth of material. Especially noteworthy are the illustrations of the kidney and the inflammatory lesions of bone. Each plate is accompanied by a concise note on the clinical history, gross appearance and microscopic structure.

There can be no question that this Atlas should be of practical use to the surgeon who so often must base his judgment and form an opinion solely on the gross morbid appearance of the lesion as it confronts him at operation. Certainly also the Atlas would be a valuable addition to the teaching equipment of any medical school. It is planned to continue publication of the Atlas until it includes all of the typical lesions that can profitably be illustrated by drawings of museum specimens. N. McL.

THE GREEK HERBAL OF DIOSCORIDES. Illustrated by a BYZANTINE A.D. 512; Englished by JOHN GOODYER A.D. 1655; Edited and First Printed A.D. 1933 by ROBERT T. GUNTHER, M.A., HON. LL.D. Pp. 701; 396 illustrations. Oxford: For author at University Press, 1934. Price, £3, 3s.

STRANGE as it may seem, there has never before been published an English translation of this most famous of all Herbals—in fact no English translation was even made until the Greek text with interlinear English was written out by the famous botanist John Goodyer between 1652 and 1655. It is interesting to speculate what the effect on Gerard, Parkinson and the other English herbalists would have been if this translation had the good fortune of Philemon Holland's Pliny and other classical translations. The present work practically represents Goodyer's translation, the manuscript of which had rested with his botanical library in oblivion in Magdalen College. The interest attaching to this celebrated "Greek work of the first century as understood in Hampshire in the sixteenth" is further satisfied by the reproductions of numerous botanical illustrations done by a Byzantine artist of about 512 A.D. And yet it seems that its chief value rests in now having a Dioscorides available in the vulgar tongue. E. K.

THE HARVEY LECTURES, 1932–1933. SERIES 28. By various contributors. Edited by DR. EDGAR STILLMAN. Delivered under the auspices of The Harvey Society of New York. Pp. 233; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.00.

THE high level of this well known series is maintained by the following articles: The Constitutional Principle in Clinical Medicine, by Julius Bauer; Similarities Between Diseases of the Vegetable Kingdom and Those of Man and Animals, by L. O. Kunkel; The Nature of the Menstrual Cycle,

by George W. Corner; Dyspituitarism: Twenty Years Later, by Harvey Cushing; The Oxidation of Hemoglobin and Other Respiratory Pigments, by James B. Conant; Contributions of Chemistry to the Knowledge of Immune Processes, by Michael Heidelberger; Recent Biochemical Studies of Liver Function, by J. C. Drummone; Humoral Transmission of Nervous Impulses, by Otto Loewi. E. K.

JAPANESE MEDICINE. By Y. FUJIKAWA, M.D. Translated by JOHN RUHRÄH, M.D. Vol. XII of Clio Medica. Pp. 114; 8 illustrations. New York: Paul B. Hoeber, Inc., 1934. Price, $1.50.

IF one reads a program of a meeting of the Japanese Society of Internal Medicine and, if at the same time the names of the participants are covered over, one would conclude that the program represented the most distinguished German, English or American medical gathering. And yet it is only about a hundred years, according to Fujikawa's interesting book on Japanese medicine, that Dr. Philipp Franz Siebold introduced German medicine into Nippon. There had been some contact with Dutch physicians in the latter part of the eighteenth century and Ryotaku Mayeno about 1770 began by himself to study the Dutch language, using several Dutch medical works and a dictionary. He mastered the language completely and with several coworkers brought out, under the title Kaitai Shinsho, a translation of the Anatomy of Johan Kulmus. Subsequently the translators with some others formed the so-called Rangaku, which means the Science of Holland (Ran, an abbreviation for Holland, and Gaku, Science). This school became the basis of the development of European science in Japan. After the Franco-Prussian War a number of German military officers came to Japan and organized medical teaching on the German model. To this day the German influence is paramount and much of the work of the native physicians is published in German, some in English.

The whole development of Japanese medicine from its beginning as an offspring of Chinese medicine to its high state of the present day is discussed concisely in Fujikawa's book, which the excellent translation by Dr. Ruhräh makes very readable. A final chapter, by Amano, deals with the work of such men as Shiga, Takamine, Kitasato, Yamagiwa, Noguchi, Hata and others whose names are known throughout the civilized world.

When one contemplates all that the Japanese have accomplished, especially since Commodore Perry's visit in 1854, one can understand their pride and their utter unwillingness to take second place to any other nation. D. R.

THE MAMMALIAN RED CELL AND THE PROPERTIES OF HEMOLYTIC SYSTEMS. By ERIC PONDER, Washington Square College, New York University. Pp. 311; 52 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 22.50.

THIS monograph, of great value for those cultivating the several fields of hematology, has the special advantage of dealing only with those topics in which the author has had extensive experince. Thus while the development of the erythrocyte, its rôle in respiration and the chemistry of hemoglobin are not included, the reader has the satisfaction of knowing that the treatment of such matters as the numbers, size, shape, structure, permeability of the erythrocyte, and its behavior during hemolysis reflects not only comprehension but also largely the results of important original contributions. Even with this self-imposed limitation, however, extensive reference has been required, two or more of the ten chapters apparently being entirely

composed in this way. Any yet incomplete consideration of the literature is the greatest fault to be found with this admirable work. Throughout, the treatment is as mathematical as is possible with a biological subject containing an unknown but considerable number of variables. Though not conducive to "light reading" or to immediate practical results (neither of which goals was sought for), it furnishes for the first time a firm basis for future comparisons and advances. The treatment of the general factors underlying cell lysis and their special application to the erythrocyte will be found especially illuminating. E. K.

THE MEDICOLEGAL NECROPSY. A Symposium held at the Twelfth Annual Convention of the American Society of Clinical Pathologists at Milwaukee, Wisconsin, June 9, 1933. Edited for the Society by THOMAS B. MAGATH, The Mayo Clinic, Rochester. Pp. 167; 63 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

MEDICOLEGAL Pathology in this country suffers from the diversity of laws on the subject in the individual states, and a consequent lack of familiarity with its details on the part of medical men. The 1933 symposium of the American Society of Clinical Pathologists (reprinted here from the American Journal of Clinical Pathology) should go far in remedying several aspects of this defect. Schultz's exposition of our medical-legal system (which might well have been longer) offers strong arguments for the replacement of the archaic, pernicious Coroner's office by the Medical Examiner. The special features of a medicolegal autopsy, its toxicology, and characteristic findings are ably, if at times gruesomely, presented. E. K.

MODERN CLINICAL SYPHILOLOGY. By JOHN H. STOKES, M.D., Duhring Professor of Dermatology and Syphilology in the School of Medicine, University of Pennsylvania, and Professor of Dermatology-Syphilology in the Graduate School, etc., with ten collaborators. Pp. 1400; 973 illustrations. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, $12.00.

THE tremendous accumulation of new material in this field has required extensive changes and additions, a revision which the author's connection with the American Syphilis Investigation has peculiarly fitted him to perform. Of the original 23 chapters, 15 have been rewritten and a new chapter on relapse and progression added. Fundamental principles and practical applications of diagnosis and treatment receive equal attention; nor is visceral or neural syphilis neglected. The present book is even more valuable than its first edition. (For Review see Am. J. Med. Sci., **174**, 705, 1927.) E. K.

MEDICINE. A VOYAGE OF DISCOVERY. By JOSEF LÖBEL, M.D. Translated from the German by L. MARIE SIEVEKING and IAN F. D. MORROW. Pp. 334. New York: Farrar & Rinehart, Inc., 1934. Price, $3.00.

A VERY readable, instructive and non-technical approach to the subject of medicine presented in 16 chapters, from the point of view of the historical development of its various branches, such as Anatomy, Pathology, Surgery, Theory of Constitution, Psychoanalysis and so on. Yet the various "ports of call" on the voyage are so well introduced by the opening chapters on medicine and biology and so closely welded together that the unity of medicine becomes apparent, whether to "intelligent layman" reader or the medical student or the busy doctor wishing to get a desirable background

for his life work. By an unfortunate translator's error, the word "typhoid" is regularly rendered "typhus," doubtless due to the German ambiguity on this point. E. K.

EARLY FORERUNNERS OF MAN. A Morphological Study of the Evolutionary Origin of the Primates. By W. E. LE GROS CLARK, D.Sc. (LOND.), F.R.C.S. (ENG.), Professor Elect of Anatomy, University of Oxford; Professor of Anatomy in the University of London, etc. Pp. 296; 89 illustrations. Baltimore: William Wood & Co., 1934. Price, $5.00.

THIS book seeks to study Man's phylogenetic origin, by visualizing the evolutionary development of the whole group of Primates. By noting and following up the trends manifest in the early generalized Primates, light is thrown on the particular trends of Man's evolution—a more valuable method than comparison with existing primates, which are all terminal products of evolutionary lines. The evidence furnished by the skull, teeth, limbs, brain and so on, methodically presented, should be of especial value to students of comparative anatomy and physical anthropology; to the general reader the chapters on the space and time distribution of the primates and their evolutionary radiations should be of most interest.

E. K.

THE ANÆMIAS. By JANET M. VAUGHAN, D.M. OXON., M.R.C.P. (LOND.), Beit Memorial Fellow, The Bernhard Baron Institute of Pathology, The London Hospital, etc. With Notes on Normal and Pathological Erythropoiesis by HUBERT M. TURNBULL, D.M. OXON., F.R.C.P. LOND., Director of The Benhard Baron Institute of the London Hospital. Pp. 248; 24 illustrations. New York: Oxford University Press, 1934. Price, $4.00.

THE extensive and productive activity in hematologic studies of the past decade has resulted in a greatly increased output not only of original articles but also of monographic reviews and "present statuses" and here we have just one more. Too short to be a complete statement (and its 350 references are admittedly incomplete and really inadequate), this booklet aims to review the clinical as well as the hematologic aspects of the 49 types of anemia included in the classification. In each type is considered etiology, symptoms, pathologic anatomy, differential diagnosis and treatment. Practical considerations and red cell diameters are stressed throughout, and the most recent literature is included. More important earlier literature is thus sometimes crowded out. Misstatements and generally discarded concepts are few, but one is surprised to find avoirdupois weights mixed with other metric measurements. Clearly expressed, with a more than average accuracy, this volume should be useful for the practitioner who wishes to keep up to date in hematology. E. K.

NEW BOOKS.

International Clinics, Vol. 2, Forty-fourth Series, 1934. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with fourteen collaborators. Pp. 317; illustrated. Philadelphia: J. B. Lippincott Company, 1934. (Price not given.)

A very interesting number, reflecting a truly international list of authors writing on important topics.

Die diätetische Behandlung der Allergie bei inneren Erkrankungen. By DR. CARL FUNCK, Chefarzt der Abteilung für Allergie und Ernährungskrankheiten am Elisabeth-Krankenhaus Köln-Hohenlind. Pp. 92. Leipzig: Johann Ambrosius Barth, 1934. Price, Rm. 2.40.

The Mammalian Red Cell and the Properties of Hæmolytic Systems. By ERIC PONDER, Washington Square College, New York University. Pp. 311; 52 illustrations. Berlin: Gebrüder Borntraeger, 1934. Price, Rm. 22.50. (Review, p. 285.)

The Medical Clinics of North America, Volume 17, No. 6 (Chicago Number—May, 1934). Index Volume. Pp. 266; 38 illustrations. Philadelphia: W. B. Saunders Company, 1934.

Lettsom. His Life, Times, Friends and Descendants. By JAMES JOHNSTON ABRAHAM. Pp. 498; illustrated. London: William Heinemann, Ltd., Price, 30/-net.

Electrokinetic Phenomena and Their Application to Biology and Medicine. By HAROLD A. ABRAMSON, M.D. Pp. 331; 106 illustrations. New York: The Chemical Catalog Company, Inc., 1934. Price, $7.50.

The Anæmias. By JANET M. VAUGHAN, D.M. (OXON.), M.R.C.P. (LOND.), Beit Memorial Fellow, The Bernhard Baron Institute of Pathology, The London Hospital, etc. With Notes on Normal and Pathologic Erythropoiesis, by HUBERT M. TURNBULL, D.M. (OXON.), F.R.C.P. (LOND.), Director of the Bernhard Baron Institute of The London Hospital. Pp. 248; 24 illustrations. Price, $4.00. (Review, p. 287.)

Early Forerunners of Man. A Morphological Study of the Evolutionary Origin of the Primates. By W. E. LE GROS CLARK, D.SC. (LOND.), F.R.C.S. (ENG.), Professor Elect of Anatomy, University of Oxford; Professor of Anatomy in the University of London, etc. Pp. 296; 89 illustrations. Price, $5.00. (Review, p. 287.)

Die Werke des Hippokrates. Part 1. Sitten- und Standeslehre für Ärzte (Price, Rm. 2.80); Part 2, Die Altbewährte Kunst / Die Kunst. (Price, Rm. 3.) Pp. 59 each. Stuttgart: Hippokrates-Verlag G. M. B. H., 1934. (To be published in 25 parts costing ca Rm. 100, card binding).

Le Barbiturisme Aigu et les Antidotismes Gardenal: Strychnine, Coramine, Alcool. From the Medical Clinic of the Hospital of St.-Sauveur à Lille. By G. CARRIÈRE, Professeur de Clinique Médicale, CLAUDE HURIEZ, Chef de Clinique Médicale, and P. WILLOQUET. Pp. 164; illustrated. Lille: A. Durant, 1934. Price, 30 frs.

The Management of Fractures, Dislocations, and Sprains. By JOHN ALBERT KEY, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine; Associate Surgeon, Barnes, Children's and Jewish Hospitals, St. Louis, and H. EARLE CONWELL, M.D., F.A.C.S., Orthopedic Surgeon for the Tennessee Coal, Iron and Railroad Company, Birmingham, Alabama, etc. Pp. 1164; 1165 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $15.00.

Spinal Anesthesia. Technic and Clinical Application. By GEORGE RUDOLPH VEHRS, M.D., Salem, Oregon. Pp. 269; 81 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $5.50.

Surgery of a General Practice. By ARTHUR E. HERTZLER, M.D., Chie, Surgeon, Halstead Hospital; Professor of Surgery, University of Kansasf and VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Pp. 602; 472 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $10.00.

Tuberculosis in the Child and the Adult. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Clinical Professor of Medicine (Department of Chest), University of Southern California, the School of Medicine; Medical Director, The Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, California. Pp. 611; 85 illustrations. St. Louis: The C. V. Mosby Company, 1934. Price, $8.50.

That Heart of Yours. By S. Calvin Smith, M.D., Sc.D. Pp. 212; 6 illustrations. Philadelphia: J. B. Lippincott Company, 1934. Price, $2.00.

Who Shall Survive? A New Approach to the Problems of Human Interrelations. By J. L. Moreno, M.D. Pp. 437; illustrated. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1934. Price, $4.00.

The International Medical Annual. A Year Book of Treatment and Practitioners Index, 1934. Fifty-second year. H. Letheby Tidy, M.A., M.D. (Oxon.), F.R.C.P., and A. Rendle Short, M.D., B.S., B.Sc., F.R.C.S., Editors, with 31 contributors. Pp. 579; 101 illustrations, 69 plates, some in color. Baltimore: William Wood & Co., 1934. Price, $6.00.

This admirable and unique volume again presents to us a review of medical advances of the past year, as seen through wise English eyes. The easy reference allowed by the alphabetical arrangement of topics is supplemented by a good index.

Clinical Miscellany. Vol. 1, 1934. By 10 contributors. Pp. 206; 37 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $3.00.

Twenty-two communications from members of the staff of the Mary Imogene Bassett Hospital, Cooperstown, N. Y., presenting reports of a variety and, in part, unusual types of cases, well worked up and commented upon.

The Life of Sir Robert Jones. A Biography of the World's Greatest Orthopedic Surgeon, the Friend of Crippled Soldiers and Children. By Frederick Watson. Pp. 327; illustrated. Baltimore: William Wood & Co., 1934. Price, $3.75.

NEW EDITIONS.

Medical Dictionary, Part I, English-German. By Joseph R. Waller, M.D., and Moritz Kaatz, M.D. Pp. 201. Fourth edition. Leipzig: Franz Deuticke, 1934. Price, M. 6.

This pocket-sized book is a complement to Waller's German-English Dictionary. Such a volume should have a useful rôle to fill. Words directly from the Latin have been omitted to save space, yet one finds such strangers as "abactio," "abaptiston," "abbot-surgeon" (Leibarzt), "ablepsy," "abomasum," "aborsement," "absterge," "acarthasia" on the first two pages. Verb. sap!

Modern Clinical Syphilology. By John H. Stokes, M.D., Duhring Professor of Dermatology and Syphilology in the School of Medicine, University of Pennsylvania, and Professor of Dermatology-Syphilology in the Graduate School, etc., with 10 collaborators. Pp. 1400; 973 illustrations. Second edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1934. Price, $12.00. (Review, p. 286.)

The Merck Manual of Therapeutics and Materia Medica. A Source of Ready Reference for the Physician. Pp. 1379. Sixth Edition. Compiled and published by Merck & Co., Inc., 1934. Price, $2.00.

This well known ready reference *vade-mecum* should require but little recommendation from reviewers. If not allowed to replace larger more comprehensive works, it can be a valuable adjunct; but this potential danger must not be forgotten by the busy practitioner who is the one most apt to use it and to commit this fault.

Pharmacology and Therapeutics. By Arthur R. Cushny, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Tenth Edition, thoroughly revised by C. W. Edmunds, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. Gunn, M.A., M.D., D.Sc., Professor of Pharmacology in the University of Oxford, Oxford, England. Pp. 786; 75 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $6.50. (Review, p. 279.)

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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AND
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HYPERPARATHYROIDISM.

During the past 15 years there has been considerable interest in the rôle of the parathyroids in the regulation of the integrity of the structure of bone. As in the case of other glands of internal secretion, the impetus for new and more exact work on the function of the parathyroids followed in the wake of the preparation of active extracts by Collip,[1] Hanson,[2] Hjort, Robinson and Tendick.[3] The results of total ablation of the parathyroid glands and the sequelæ of an increase in the amount of the hormone elaborated by these glands has been studied in man and animals in a number of laboratories and clinics. Despite the volume of work done in this field, the exact action of the parathyroid hormone is still not clear. Many facts have been discovered regarding this intricate mechanism, but the complete picture has not been painted due to a lack of many important details. Data from the experimental laboratory have contributed in a very significant manner to the recent advances made in the diagnosis and treatment of conditions arising from disturbances of parathyroid function.

The advances made in the clinical knowledge of conditions arising from alterations in function of the parathyroid glands have been quite remarkable. Conditions for which there was little hope of alleviation and less thought of an explanation of the cause now have a less pessimistic outlook. The number of articles in the medical literature dealing with the diagnosis and treatment of parathyroid dysfunction has become so great that a comprehensive survey of these in this review is not possible. Several excellent reviews of this subject have already been published (Thomson and Collip,[4] and Jaffe[5]). It is intended that this review be in the nature of an exposition of certain results of experimental effort and clinical experience germane to the surgical treatment of diseases arising from disorders of parathyroid function. For a more complete discussion of the relationship of the parathyroid glands to calcium and phosphorus metabolism the reader is referred to the review of Thomson and Collip.

The parathyroid glands are small lenticular bodies, measuring from 2 to 8 mm. in length, and lying usually in the neighborhood of the posterior or inferior surface of the thyroid gland. Normally they are firmer than the thyroid gland. In the young they are light pink in color and in older individuals they vary from pink to yellowish gray. While generally found in proximity to the thyroid, there is no relationship to this organ either embryologically or functionally. The thyroid gland arises from the ventral median diverticulum of the pharynx cranial to the second branchial cleft arches, and the parathyroid bodies originate from an entodermal anlage at the 3d and 4th branchial arches. It is thus evident that embryologically they are more closely related to the thymus. Unlike the thyroid, the parathyroids are paired structures, the pair arising from the 3d arch descending more caudad to find their usual position on the dorsolateral aspect of the lower pole of the thyroid gland, the pair arising from the 4th arch descending a much shorter distance to lie close to the superior pole of the thyroid. We have not been able to find any authentic report of their presence within the substance of this structure. The pair from the 3d arch migrate downward with the thymus, in some instances retaining their attachment to the thymus and come to rest attached to or imbedded in the thymus deep in the mediastinum. If the attachment to the thymus is broken early in their development, the glands may be found to lie quite high, sometimes being found as high as the level of the third arch. While the parathyroid glands viewed on an embryologic basis should be paired structures, 2 lying on either side of the midline, actually the number found has been described as from 1 to 12. The variations found may be explained on a basis of fusion, or retrogression of certain of the rudiments, and a splitting in other instances of the rudiments into several components.

The variability in position and number of the parathyroid glands has been well emphasized in a study of human material by Heinbach.[6] In careful dissections made on 25 human cadavers, Heinbach found from 2 to 6 parathyroids in each case, the position varying widely. The most common position was upon the medial half of the dorsolateral surface of the lateral lobes of the thyroid gland, between the common carotid artery and the inferior constrictor muscle of the pharynx above and the esophagus below, lateral and dorsal to the recurrent laryngeal nerve but not in intimate relationship to it. The parathyroid glands were not, as a rule, adherent to the capsule of the thyroid, but lay most frequently in the areolar tissue outside the true capsule. In addition to careful dissections to study the position and number of the parathyroid glands, Heinbach reviewed the literature on this subject and found similar variations reported by other authors.

The blood supply of the parathyroid glands has been studied by Curtis,[7] and Curtis and DeQuervain,[8] who found that these bodies were supplied mainly by the inferior thyroid arteries. However, by injection methods these authors found that even though the inferior thyroid was ligated, the injection mass found its way into the parathyroids in abundance. This work explains why tetany does not result from ligation of the inferior thyroid artery during the course of thyroidectomy, since the parathyroids are amply supplied by a col-

lateral circulation from the vessels of the larynx, pharynx, esophagus, trachea and the cervical fasciæ.

The work of Gley,[9] in 1892, showed that the extirpation of the parathyroid glands in the dog resulted in tetany. Subsequent work has shown that associated with and preceding the onset of tetany the serum calcium is definitely reduced and the inorganic phosphorus excretion in the urine is decreased. Unless the animal is treated with potent extracts of the gland, with calcium or vitamin D preparations, it soon dies.

The injection in a normal dog in sufficient amounts of an active extract of the parathyroid glands results in a gradual but marked increase in the serum calcium which after a time reaches a peak and then tends to level off or drop slightly. The inorganic phosphorus in the blood after such an injection decreases except when toxic doses of the extract are administered. Then, due most likely to suppression of urinary excretion, the phosphorus of the blood increases. Associated with the changes in the level of calcium and inorganic phosphorus in the blood there is an increased excretion of both these substances through the kidneys. These findings are clear-cut and offer no point of controversy. There is, however, considerable controversy concerning many points, such as the exact location of the source of the calcium and phosphorus excreted, above that ingested. Bauer, Aub and Albright[10] suggest that the bone trabeculæ provide a mobile store of calcium which is decreased by parathyroid hormone administration. A calcium-poor diet in a normal animal also tends to draw on this store of calcium, a calcium-rich diet tending to replace it. Exception has been taken to the statement that it is from the trabeculæ from which calcium is lost after parathyroid hormone administration (Bodansky and Jaffe,[11] and Gyorgy[12]), but all authors place the stores of easily mobilized calcium in the bony skeleton.

The serum phosphatase has been shown to be high in osteitis fibrosa cystica, produced experimentally in guinea pigs by parathyroid hormone administration (Bodansky and Jaffe[13]). Similar findings with regard to serum phosphatase have been reported in certain other diseases of the bone, *e. g.*, rickets, generalized osteitis fibrosa cystica and osteitis deformans (Hunter[14]). Following injections of parathyroid hormone, the concentration of bone phosphatase is decreased (Page[15]).

Many instances of the association of parathyroid adenomata with certain diseases have been reported since Askanazy[16] published a case of osteitis fibrosa cystica with a tumor which was probably of parathyroid origin. Three years after the publication of Askanazy's case, Erdheim reported a case of puerperal osteomalacia with a large parathyroid tumor. Erdheim felt that the tumor was the result of the bone disease, and that it represented compensatory hyperplasia. Hoffheinz[17] reviewed 45 cases of various disorders of bone collected from the literature, together with a case of osteitis fibrosa cystica which he had autopsied, all of which showed enlargement of the parathyroid glands. Of these cases, 17 had definite osteitis fibrosa cystica, while in 8 a diagnosis of osteomalacia was made. Renal calculi were present in a number of instances. Barr and Bulger[18] extended the number of cases of bone pathology with associated parathyroid enlargement by the addition of 29 other cases. Hoffheinz commented on the

association of parathyroid enlargement and bone disease chiefly on the basis of Erdheim's original concept that the changes in the parathyroid were a compensatory mechanism. It may seem unusual that the true mechanism was not earlier recognized and the association of certain bone diseases and the enlarged parathyroids encountered in these did not lead to treatment by parathyroidectomy at an earlier date. This may possibly be explained on the basis that enlarged parathyroids had been reported in patients in whom there was no demonstrable bone pathology. In addition, many cases of bone disease, notably osteomalacia, had been carefully investigated and found to have no parathyroid enlargement, so that any relationship which may seem apparent now could not have been clearly evident twenty years ago. Nevertheless, Schlagenhaufer[19] did suggest that the parathyroids be removed in some of the malacic diseases. Since experience has shown that the best results have been obtained in osteitis fibrosa cystica, it is possible that an attempt at extirpation of the parathyroids if done at that time might have served only to cloud the issue, had the parathyroidectomy been performed in a patient suffering from osteomalacia.

The first case reported in which a parathyroid tumor was removed for treatment of bone disease was published by Mandl,[20] in 1926. This patient had, previous to the removal of an adenoma of the parathyroid, a parathyroid transplant, which it was thought might relieve the condition, on the basis of Erdheim's theory that the disease was due to parathyroid deficiency. When implantation therapy failed, Mandl explored the neck of the patient and removed a parathyroid adenoma. The following is Mandl's description of his case:

The patient was a street-car conductor, aged 38 years, having a sister who suffered from osteitis fibrosa cystica. He became ill 5 years previously, following a luetic infection. His chief complaint was increasing fatigue in his lower extremities. He became so weak that it became necessary for him to stop work. He had many types of treatment, but except for short remissions the disease progressed. In 1924 he had to resort to the use of crutches. In October, 1924, Roentgen ray showed osteitis fibrosa cystica of the pelvis and femora. He was given thyroid and parathyroid extracts without arresting the progress of his disease. In December, 1924, he suffered a spontaneous fracture of his left femur. In June, 1925, Mandl saw him in his clinic. He was unable to use his lower extremities. Lying down he could not lift his legs or bend his knees. He had pain in his pelvis and legs, and said he could neither stand nor sit, as he felt his pelvis was too weak. He was quite emaciated and, most important, he excreted so much calcium in his urine that it settled out on standing. This excretion of excess amounts of calcium the patient had noted for many months. These symptoms were worse in the colder seasons. On July 2, 1925, 4 parathyroid glands were removed from a dying patient and transplanted into the patient, but he showed not the least improvement. Microscopic examination of the tissue was not done.

Careful search was later made for a palpable tumor but none was found. The patient was willing to submit to a careful search for a parathyroid tumor in the hope that its removal would influence the course of his disease. On July 30, 1925, Mandl removed a yellowish-

brown tumor, almond shaped, sharply demarcated from the surrounding tissue, measuring 25 by 15 by 12 mm., from the area between the left lobe of the thyroid gland and the trachea. It was rather firmly attached to the recurrent laryngeal nerve and was dissected free. It was shelled out from a connective-tissue capsule and had small elevations on its surface.

Examination of the other parathyroid glands revealed the presence of 3 normal appearing glands. The wound healed by primary intention, a temporary recurrent laryngeal nerve paralysis resulting following the operation.

The gland which was removed revealed parathyroid tissue. The alveolar epithelium showed a mosaic pattern with the cells lying one under the other, separated by a fine red line. The protoplasm of the alveolar cells was water-clear and contained nuclei lying free and which contained fine eosinophilic granules. The nuclei were generally bright, round, vesicular and variable in size. Many of the nuclei were 5 times as large as others. The appearance of the alveoli gave a palisading effect, most of the alveoli appearing completely solid. Occasionally a lumen was noted with thin eosin-red contents. Hemorrhage was noted in areas, as well as hematogenous pigment in the connective tissue. Normal parathyroid tissue could not be seen in the section.

The postoperative course showed a marked change in the patient. A few days after the operation it was possible to see with the unaided eye the difference in the excretion of calcium in the urine (9.6 mg. % as compared with 54 mg. % before operation). Four months after operation the bones showed a marked increase in the calcium content; subjectively the patient was much better also. The patient was able to be about with a crutch and a cane, which was impossible for many months before the operation. The pains in the pelvis and legs were gone, and he could move the extremities. He gained weight and looked better, even in a season when ordinarily he would suffer most.

The recognition of the relationship between osteitis fibrosa cystica and parathyroid gland disease in America was made, in 1926, by DuBois.[21] The patient, a sea captain, aged thirty years, who was seen by DuBois in the Bellevue Hospital in New York, has been extensively discussed. A most complete and painstaking study of his case by Hannon, Shorr, McClellan and DuBois,[22] Bauer, Albright and Aub,[23] McClellan and Hannon,[24] and Churchill and Cope[25] has undoubtedly shed more light on the clinical picture of hyperactivity of the parathyroid glands than any other case.

In 1929, Barr, Bulger and Dixon[26] published observations on a case of osteitis fibrosa cystica in which there was an amelioration of symptoms following the extirpation of an enlarged parathyroid gland.

From a review of the literature and observations on the case these authors felt that they were dealing with a definite clinical entity in which (1) rarefaction of bone, (2) multiple cystic tumors in the bone, (3) muscular weakness and hypotonia, (4) abnormal excretion of calcium, (5) formation of calcium stones in the kidneys and (6) a high serum calcium was present. They chose the name of hyperparathyroidism for this symptom complex because of the association of hyperplastic parathyroid tissue and signs suggesting an excess of the hormone

of the parathyroid glands in the body. This term seems to be a very happy one and has been universally accepted. On the basis of later work it became evident that there were many conditions which might fit partially into the chain of symptoms and signs designated by Barr, Bulger and Dixon,[26] which were not really the result of parathyroid hyperactivity but which have later come to be classed as hyperparathyroidism by certain writers. Bauer[27] has presented a more detailed and complete picture of hyperparathyroidism which narrows the clinical picture to include only the bone disorder known formerly as von Recklinghausen's disease or osteitis fibrosa cystica. We quote Bauer's criterion in full: "Hyperparathyroidism is a disease characterized by definite alterations in the calcium and phosphorus metabolism as well as by certain symptoms and signs. The alterations in the calcium and phosphorus metabolism are:

"1. *An Elevated Serum Calcium.* Serum calcium values as high as 23.6 mg. per 100 cc. have been reported. The normal serum calcium varies between 9.5 and 10.5 mg.

"2. *A Decreased Serum Phosphorus.* Values as low as 1.4 mg. per 100 cc. have been observed, in contrast to normal values of 4 to 5 mg.

"3. *An Increased Calcium Excretion.* The increased excretion of calcium is entirely urinary, the fecal excretion being unaffected.

"4. *An Increased Phosphorus Excretion.* The increased excretion of phosphorus is also entirely urinary. The increased excretions of calcium and phosphorus in 1 reported case were of the same magnitude as those in a normal individual receiving 100 units of an active parathyroid extract per day.

"These alterations in the calcium and phosphorus metabolism may be accompanied by any or all of the following symptoms and signs: (1) polydipsia; (2) polyuria; (3) weakness and loss of strength; (4) constipation; (5) loss of appetite; (6) loss of weight; (7) indefinite muscle and joint aches and pains (commonly diagnosed rheumatism, arthritis or neuritis); (8) bone tenderness; (9) frequent fractures, often following slight trauma; (10) decreased excitability of the nerves; (11) skeletal shortening; (12) kyphosis; (13) bone tumors, frequently diagnosed epulis of the jaw or giant-cell tumor in other bones; (14) kidney or ureteral stones (usually bilateral); (15) characteristic *X*-ray findings,—such as generalized decalcification, bone tumors, multiple bone cysts, fish-type vertebral bodies, etc.; (16) frequently anæmia with leukopenia."

Unquestionably there are other conditions in which enlarged parathyroid glands have been associated with bony changes, as renal rickets (Langmead and Orr[28]), osteomalacia (Erdheim[29]), chronic interstitial nephritis (Harbitz[30]), multiple myelomata (Barr and Bulger[18]), and carcinoma (Klemperer[31]).

Hyperplastic or adenomatous parathyroid glands in these conditions, however, should be considered as a rare finding. In the case of generalized osteitis fibrosa cystica enlargement of the parathyroid glands is the rule. This is exemplified by the case of the sea captain studied by DuBois,[21] Hannon, Shorr, McClellan and DuBois,[22] Bauer, Albright and Aub,[23] McClellan and Hannon,[24] and Churchill and Cope,[25] in whom repeated searches were made for a period of 6 years before a parathyroid adenoma was found by Churchill.

Ballin[32] has attempted to broaden the scope of the term hyperparathyroidism to include Paget's disease and arthritis deformans. This view has been rather strenuously contested by Bauer[27] and Jaffe,[5] chiefly on the basis that in these conditions increased phosphorus and calcium excretion are not found. Whether or not other bone lesions may eventually be found to be associated with true hyperparathyroidism remains to be seen. At the present time the evidence is not convincing.

The renal lesions associated with hyperparathyroidism have been described by Albright, Baird, Cope and Bloomberg.[33] These authors present 3 different types of renal involvement in hyperparathyroidism. They designate their Type 1 as a pyelonephritis, secondary to formation of calcium phosphate stones in the renal pelvis, and suggest that patients with renal stones should be examined for evidences of hyperparathyroidism. Type 2 they designate as those cases having old deposits of calcium in the kidney parenchyma. Type 3 comprise those cases which show signs of acute parathyroid poisoning. The kidney deposits of calcium are found in the parenchyma without chronic renal changes. These cases suffer from anuria and die within a few days.

The case of the sea captain who was the subject of much study did not show evidence of renal calculi when first seen. Calculi did, however, develop during the further course of his disease and showed evidence of Type 2 renal involvement as described by Albright *et al.* The question of whether the calculi which are found in cases of hyperparathyroidism will disappear after parathyroidectomy is intriguing. The possibility of causing solution of these stones by a high phosphorus diet or by the use of sodium acid phosphate, as suggested by Albright, Bauer, Claflin and Cockrell,[34] is to be considered, but the possibility of causing further kidney damage with decreasing phosphorus excretion and an increase of phosphorus and calcium in the blood must also be considered. It is interesting that this phase of the subject has not received more widespread attention. It is probable that, should these patients reach a normal phosphorus-calcium metabolism after the extirpation of the offending parathyroid gland and live for several years in good health, there will be reports concerning the status of the kidney stones. In a personal communication, I. Y. Olch reports that a case upon whom he removed a tumor of the parathyroid 4 years ago has shown a definite decrease in the size of her kidney stone.

Hyperparathyroidism as a clinical entity is apparently on a sound basis when the diagnosis is made not only upon the appearance of the bone lesions, but also upon careful metabolic studies. So far the treatment is surgical, since no case has shown improvement on a strictly medical régime. The limits of the clinical entity are clearly defined. Cases of generalized osteitis fibrosa cystica fit into the entity of hyperparathyroidism well. Other bone diseases do not show the striking recovery after parathyroidectomy as do the cases of osteitis fibrosa cystica. Whether other bone diseases will be found to fit the term hyperparathyroidism, it is difficult to say, but in order to introduce any other disease entity into this term, there must be careful metabolic studies made which show that the disease is similar to the conditions found when there is an excess of the hormone of the parathyroid in the organism. The diagnosis of hyperparathyroidism cannot be made save after a careful study of calcium and phosphorus metabolism.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF

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THE CEREBRAL CENTERS OF VISION.

Interest in the clinical and experimental investigation of cortical localization of the visual functions was revived by the studies of Gordon Holmes and others on visual defects following war injuries to the occipi-

tal lobe. Holmes[1] stated that complete destruction of the striate area on one side caused a complete homonymous hemianopsia through the center of fixation. This finding seemed to contradict the theory of bilateral representation of the macula in the occipital cortex, which theory had been advanced to explain the usual finding in occipital lobe lesions of homonymous hemianopsia with sparing of the macula. Holmes thought that the sparing of the macula usually found in vascular lesions was therefore probably due to overlapping of the arterial supply to the two cuneal areas. He also found that visual hallucinations of the unformed type in the blind field were often associated with lesions of the visual cortex. Holmes was able to demonstrate that defects in the lower field of vision resulted from lesions above the calcarine fissure, that defects in the upper fields were associated with lesions below the calcarine fissure, and that central scotomata, or defects in the macular field, were found in lesions at the occipital pole. A lesion at one occipital pole caused homonymous paracentral scotomata, while injuries to the anterior part of the striate area were followed by peripheral field defects.

These findings lent strong clinical support to the theory of definite and detailed representation of individual portions of the retina in exactly localized areas of the striate cortex. Numerous investigative studies have been undertaken to furnish anatomic and histologic proof of this theory.

Brouwer and Zeeman[2] studied the nerve fiber and cell degenerations in the primary visual centers following small, experimentally produced lesions of the retina in monkeys. They found that the fibers from the upper half of the retina terminated in the medial part of the external geniculate body, while those from the lower half terminated in the lateral portion. The macular fibers were found to have a very wide distribution in the central part of the geniculate. The peripheral parts of the retina, but not the macula, were found to have small projections in the anterior quadrigeminal body. No visual fibers could be traced into the pulvinar. Brouwer[3] had already carried out similar investigations in rabbits and had found an equally definite though somewhat differently located representation of the retinal quadrants in the external geniculate body. Putnam and Putnam, working in Brouwer's laboratory, then excised portions of the striate cortex in rabbits and followed the resultant fiber degenerations back to the external geniculate body. They were able to demonstrate that there was a fixed and definite anatomic projection of the retinal quadrants on the striate cortex and that there was no connection between the striate cortex on one side and the external geniculate of the opposite side.

Following up this work and correlating it with the careful histologic study of two human brains, Putnam concluded that, in man, (1) the optic radiation lies in the inferior longitudinal fasciculus and occupies all of it; (2) the upper quadrant of the retina is projected on the mesial limb of the geniculate body, on the upper portion of the inferior longitudinal fasciculus (optic radiation) and on the upper anterior portion of the striate cortex; (3) the lower quadrant of the retina is represented laterally in the geniculate and inferiorly in the radiation and striate cortex; (4) the macula is represented between the upper and lower fibers in the upper portion of the posterior half of the geniculate and in the posterior part of the striate cortex where its representation is

extensive, and (5) there are apparently no fibers crossing in the corpus callosum from one visual tract to the opposite striate cortex by means of which macular sparing in occipital lobe hemianopsia can be explained.[5]

Putnam was able to show further[6] that the calcarine fissure does not divide the striate area accurately in two and that it is an unreliable landmark for orientation, more of the visual area usually lying below than above it. He estimated that about 65% of the fibers in the optic nerve arise from the central area of about 2.7 mm. around the fovea, corresponding to about 25° in the visual field, and that about 47% of the optic radiation carries macular fibers, these fibers occupying the center of the radiation. The macular area in the cortex extends about 2 to 3 cm. anterior to the occipital pole.

That the area of the striate cortex reserved for macular vision is relatively very large was shown by Brouwer in a case of homonymous hemianopsia with macular sparing due to a small lesion in the frontal part of the striate area.[7] Brouwer concludes that the caudal half of the calcarine cortex along with the lateral surface of the occipital lobe serves exclusively for macular projection and that the small frontal area serves for peripheral vision. He believes that the macular area extends farther frontal between the areas for the upper and lower halves of the retina than is commonly believed. Almost the whole of the striate area in man lies on the medial side of the occipital lobe.

Poljak carried on an extensive series of investigations in which he studied the degenerations caused by experimental lesions, both in the external geniculate and optic radiation, and in the striate cortex in monkeys.[8] He found that the optic radiation was divided into (*a*) an upper horizontal branch which commences in the mesial segment of the geniculate, carrying fibers from the upper retina and reaching the upper lip of the calcarine fissure by circling above the posterior horn of the lateral ventricle; (*b*) a lower horizontal branch from the lateral segment of the geniculate and lower half of the retina which goes to the lower lip of the calcarine fissure below the posterior horn of the lateral ventricle, and (*c*) an intermediate or vertical branch carrying macular fibers to the lateral face of the occipital lobe and to its tip. The most anterior part of the striate cortex was shown to be connected with that portion of the geniculate body which receives fibers from the farthest periphery of the retina. By producing minute lesions in the striate cortex and studying the resultant degenerations, Poljak was able to prove that not only each quadrant of the retina has its separate cortical representation, but each minute portion of the retina is represented in the cortex separately. He demonstrated that complete extirpation of the striate area on one side produced total degeneration of the external geniculate on the same side but had no effect on the external geniculate of the opposite side.

From these data there would seem to be no foundation for the belief in a bilateral cortical representation of the macula. However, it is known that, clinically, homonymous hemianopsia with macular sparing is common in lesions of the occipital lobe. Davison, Goodhart and Needles[9] report that closure of the calcarine artery will cause partial hemianopsia, inferior quadrantanopsia being present in lesions above the calcarine fissure and superior quadrantanopsia in lesions below the fissure. They state that, according to Foix, complete closure of the

left posterior cerebral artery will result in hemianopsia and alexia. Penfield and Evans[10] find that temporal lobectomy in man will cause complete homonymous hemianopsia without sparing of the macula, due to removal of the optic radiation, while occipital lobectomy results in homonymous hemianopsia with macular sparing. German and Fox[11] also found homonymous hemianopsia with macular sparing after occipital lobectomy. In their case all of the area striata was removed except a small portion along the stem of the calcarine fissure. Penfield and Evans, and German and Fox conclude, therfore, that in man there must be a bilateral cortical representation of the macula, or else there must be representation of the macula but no representation of the periphery of the retina anterior to the level of their lobectomy. H. P. W.

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